SÍNTESIS EMPÍRICA DE META-ANÁLISIS, TÉCNICAS DE OPTIMIZACIÓN MULTI-OBJETIVO Y MINERÍA DE DATOS APLICADAS AL DIAGNÓSTICO DE LA ENFERMEDAD DE ALZHEIMER

UNIVERSIDAD
DE BURGOS

Olalla Saiz Vázquez

Síntesis empírica de meta-análisis, técnicas de optimización multi-objetivo y minería de datos aplicadas al diagnóstico de la Enfermedad de Alzheimer

Directores: Silvia Ubillos Landa y Joaquin Antonio Pacheco Bonrostro

Universidad de Burgos

2023

A mis padres y mi sister

Iris…

En memoria de mi abuela

AGRADECIMIENTOS

Quiero aprovechar para rendir homenaje a todas aquellas personas que me han ayudado y acompañado durante este largo aprendizaje. Todo el esfuerzo realizado para concluir esta tesis, en parte, es gracias a todos los que me habéis apoyado. Por esta razón, estas palabras os las dedico con enorme cariño a cada uno de vosotros.

Primeramente, agradecer a mis directores de tesis: Silvia, gracias por ayudarme a crecer como investigadora y como persona, por ir acompañándome en cada paso del camino haciendo de mí una persona independiente y menos inocente. Por enseñarme a ir despacio para poder ver detenidamente todo lo que me rodea y darme cuenta de todo lo que he disfrutado por el camino. El camino ha sido largo, pero me siento orgullosa de lo que hemos construido juntas y del apoyo constante que me has brindado en todo el proceso, sin ti, no hubiera sido posible. Joaquín, las oportunidades que me has dado han sido incomparables, gracias por apostar en una rama de la que no eres especialista, pero que has querido aprender desde el primer minuto, gracias por prestar tu apoyo siempre que lo he necesitado. Silvia… Joaquín… es difícil que estas breves palabras puedan mostrar todo el agradecimiento que siento hacia vosotros, no sólo en lo que respecta a este trabajo, sino también en lo personal.

Al Doctor Andrea Fabbo, Alessandro Lanzoni y todos los compañeros que me acompañaron durante 3 meses en Italia, por haberme acogido con tanta generosidad. De cada uno de vosotros me llevo lo mejor y todo lo que me habéis enseñado en un periodo que recordaré como algo duro, pero como una experiencia inconmensurable.

Alicia Puente (Ali), gracias por todas esas tardes de trabajo, por tu enseñanza, por los cafés online, por tu paciencia, por explicarme con detalle cada error y por ser tan exigente conmigo. En definitiva, gracias por participar tan activamente en el desarrollo de esta tesis Me llevo tantas cosas de lo que hemos compartido… Silvia Casado, gracias por tus ratos de trabajo y todo el aprendizaje.

Hoy especialmente me acuerdo de mi familia, abuela, allí donde estés… ojalá esta investigación pueda ser útil para seguir investigando en esta enfermedad y evitar el sufrimiento de usuarios y familias que soportan esto cada día en el mundo. Al resto de mis abuelos, gracias por entender, aunque solo fuera una pequeña parte, lo que hacía cuando me pasaba horas y horas delante del ordenador.

A mis padres, por haberme forjado como la persona que soy, perseverante, trabajadora y exigente, valores que han hecho posible terminar este proyecto. Soy lo que soy gracias a vuestros esfuerzos y sacrificios. Gracias por impulsarme a ser mejor cada día y lograr con éxito culminar este proyecto. A mi sister, que vive en la sombra apoyándome y que está siempre que la necesito. Gracias por tu presencia, por tus conocimientos de enfermería, por dejarme interrumpir tus estudios y en definitiva por tener siempre tiempo para tu hermana mayor. Contigo me doy cuenta de lo afortunada que soy por tener una hermana. Iris, desde que te conocí he cambiado, me diste el último empujón que necesitaba para terminar esto, gracias por acompañarme en el camino y reforzarme en todos los éxitos. Gracias por ayudarme a dosificar entre el trabajo y el ocio, por darme la mano y guiarme en momentos oscuros e impulsarme a seguir sumando.

En estos momentos también recuerdo a todos mis amigos. Tania, sabes que la portada de la tesis es lo mejor que tiene. Urko, qué decir de esas noches de karaoke en el pueblo… Chema, sabes que eres un gran amigo y el que mejor me escucha. Alberto, gracias por mantenerte cerca en la distancia… Diego y Miri, gracias por esos ratitos juntos. Maria y Rocio, esos paseos por Burgos, esas cenas… gracias por acoplaros a mis horarios y motivarme siempre a no desviarme del camino y a seguir creciendo como profesional, por haber hecho de esta tarea algo sostenible y soportable solo con vuestra compañía. A mis compañeras de equipo, que son mi escape semanal para desconectar y hacer lo que más me gusta, gracias por hacerme disfrutar de cada momento con cada una de vosotras. A mis ukes de karate… Judit,

gracias por ayudarme con el inglés cuando se me atravesaba algún texto y a mis compañeros de la Universidad de Burgos, sobre todo a Montserrat Santamaría y a Valeriana Guijo que me han ayudado a seguir hacia delante, orientándome y dándome los mejores consejos y me han dado apoyo moral e instrumental cada vez que lo he necesitado.

ÍNDICE

ÍNDICE DE TABLAS

ÍNDICE DE TABLAS DE ANEXOS

ÍNDICE DE FIGURAS

ÍNDICE DE FIGURAS DE ANEXOS

INTRODUCTION

INTRODUCTION

On November 3, 1906, Alois Alzheimer presented a communication about a peculiar disease recorded in the ex-cerebral section of the brain. The patient who had suffered from this disease was named Auguste Deter, and during his last years of his life he presented unique characteristics of dementia (1). This was the first scientific description of the Alzheimer's disease, although some historical data have been found from as far back as 500 B.C. There are other references to dementia in ancient Greece and the Roman Empire. Cicero, in one of his works, describes the loss of judgment associated with age. In the Roman Empire, it was Aurelius Cornelius who succeeded in having dementia considered a serious disease. Later, the physician Arateus of Cappadocia established the first classification of dementias and divided them into chronic and acute. Between 1894 and 1915, focal cerebral atrophy began to be studied. But if there was a turning point in the discovery of Alzheimer's disease (AD), it was in 1901 when the German psychiatrist and neurologist Alois Alzheimer began to treat a 51-year-old patient who, for no reason, presented memory problems and behavioral alterations (hallucinations, delusions, etc.). When Alzheimer studied the brain of this patient, he noted the existence of peculiar lesions and peculiar anomalies in the neuronal structures of the brain (2). This study, published in 1907, was the basis for the clinical picture of what in 1910 would become known as Alzheimer's disease. Alzheimer published a second study in 1911(3). Later, in 1973, Benjamin Rush published the data of a clinical case that matched the symptomatology of AD in the United States (2).

AD follows a progressive degenerative course characterized by an insidious progression whose symptomatological manifestations usually appear in a staggered manner. As the disease progresses, different cognitive, functional, and psychiatric symptoms characteristic of Alzheimer's-type dementia appear in different stages (3). Consensus has been reached on the establishment of three stages of disease progression (mild, moderate, and severe). The

progression of the disease depends on many factors, including the age of the user, the care and treatment received, the environment in which it develops, or the existence of other pathologies that may influence the aggravation of AD (4). The duration of AD is highly variable, with some users dying prostrate within 4 years of the onset of the disease, and others surviving for more than 12 to 15 years (5).

The main signs and symptoms that characterize AD are cognitive alterations, behavioral alterations, and neurological alterations (6). Cognitive disorders may include memory impairment (the main and most characteristic symptom of the disease), language impairment, agnosia, apraxia, disorientation, and impaired executive function. Behavioral disturbances can include delusions, hallucinations, mood swings, neurovegetative function disturbances, and psychomotor activity disturbances. Neurological signs of AD include extrapyramidal signs, dyskinesias, myoclonias, seizures, gait disturbances, and pyramidal signs (1).

STRUCTURE

STRUCTURE

This thesis aims to bring health professionals closer to AD. In this context, some of the risk factors that influence AD will be analyzed, since every year there are scientific advances in this field that explore this complex disease. AD ranks as the seventh most frequent cause of death, with a total of 13,045 people dying in 2021. Among these people 3,835 were men and 9,210 were women.(7).

This paper is structured in two main sections. **Section 1** consists of a meta-analytic review of the different risk factors that appear in the literature directly related to AD, and **Section 2** analyzes some of the risk factors using heuristic optimization, data mining, and a multi-objective approach.

In the first section, **Chapter 1** describes some of the main risk factors found in the scientific literature. From there, the factors to be analyzed throughout the thesis are selected: cholesterol, depression, blood pressure and stroke. **Chapter 2** examines the relationship between cholesterol and AD. Dyslipidemia, which has been identified as a risk factor for AD, refers to abnormal levels of lipids or lipoproteins in the blood, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and finally triglycerides (TG) and total cholesterol (TC) (8). **Chapter 3** discusses the relationship between depression and AD. Depression is one of the most common diseases that afflict the elderly, with an estimated prevalence of 6-20% in this group (9). There are numerous studies where the relationship between depression and the development of AD has been studied. Thus, studies conducted by Santa Bárbara (9), Ford(10), Kuring(11), Cherbuin(12), Diniz(13), and Gao(14) all show strong positive associations between depression and AD. No meta-analytic studies have been found that reject this relationship or that confirm a negative relationship between depression and the development of AD. **Chapter 4** studies the relationship between blood pressure with AD for which there are still no conclusive

results. Indeed, there is much debate in the scientific literature about the relationship between these two factors. Some studies associate vascular dementia with hypertension, arteriosclerosis, and stroke, and positively relate these factors to the development of AD (15). Along the same lines, another cardiovascular factor, blood pressure, could be related to the development of AD. **Chapter 5** examines strokes as another risk factor. Despite significant improvements in primary prevention and acute treatment in recent decades, strokes continue to be a devastating disease (16). Due to the increasing size and age of the world's population, the incidence of strokes is increasing dramatically. In fact, epidemiological data indicate that 16.9 million people suffer a stroke each year, representing a global incidence of 258 / 100,000 / year, with marked differences between high- and low-income countries, and an age-adjusted incidence 1.5 times higher in men than in women (17). Strokes have long been associated with AD, but the link remains controversial and unproven (18). Some studies explain the relationship by the brain changes that occur when a stroke occurs which lead to the clinical expression of cognitive impairment and dementia (19,20).

In **Section 2**, a study of heuristic optimization, data mining and a multi-objective approach is carried out. This section is divided into two chapters. In **Chapter 6**, the objective is to develop a model generating system for medical diagnostics. Different variable selection methods (filter, wrapper, and embedded) have been used within linear models that support the specific method type and that make high accuracy predictions using features of different variables. The application possibilities of supervised classification are expected to be very broad, especially in the medical-health field (aiding diagnosis and prevention). Therefore, the aim is to find a classification method that can allow, based on its characteristics (classifying variables, criteria, predictors, or explanatory variables), to classify an individual in one of the previously established groups (Group 1 (People diagnosed with AD) and Group 2 (People not diagnosed with AD)) by means of an optimal decision rule, with the objective of getting

it right as many times as possible. This is done using only information provided by a set of variables. To achieve this, the discriminant factors are calculated and the central values of each of the groups (the vectors formed by the means of each discriminant factor) are found. In **Chapter 7**, different classifiers are used – the Support Vector Machines model (SVM), the logistic regression model (LR), and the discriminant analysis model (LDA) – which are applied to the method developed in Chapter 6 to diagnose AD in the elderly from a matrix with multiple data and variables.

SECCIÓN 1

FACTORES DE RIESGO ASOCIADOS A LA ENFERMEDAD DE ALZHEIMER: REVISIÓN SISTEMÁTICA DE META-ANÁLISIS Y ESTUDIOS META-ANALÍTICOS

CAPÍTULO 1

"Cuando recordar no pueda, ¿dónde mi recuerdo irá? Una cosa es el recuerdo y otra cosa recordar."

Antonio Machado

Saiz Vazquez O, Ubillos Landa S, Puente Martínez A, Antonio Pacheco Bonrostro J y Casado Yusta S. Síntesis empírica de meta-análisis de los factores de riesgo modificables de la Enfermedad Alzheimer. En: Pacheco Bonrostro J, Cuesta Gómez JL. VII Jornadas de Doctorandos de la Universidad de Burgos. Burgos: Servicio de Publicaciones de la Universidad de Burgos; 2021.p. 365-685.

CAPÍTULO 1: SÍNTESIS EMPÍRICA DE META-ANÁLISIS DE FACTORES DE RIESGO MODIFICABLES DE LA ENFERMEDAD ALZHEIMER

RESUMEN

Introducción: La Enfermedad de Alzheimer (EA) consiste en un trastorno neuro-cognitivo asociado a la pérdida funcional y cognitiva de las personas que lo padecen. La identificación de factores que pueden modificar el curso de la EA es fundamental para poder intervenir sobre ellos a fin de prevenir la enfermedad y/o ralentizar su avance. Por ello, se ha realizado una síntesis empírica de los meta-análisis de los factores modificables de la EA.

Objetivo: Actualizar y sintetizar la evidencia empírica aportada por los meta-análisis sobre el peso de los factores de riesgo modificables de la EA para posibilitar un tratamiento de mantenimiento y mejora eficiente de las capacidades físicas y cognitivas a través de la intervención no farmacológica.

Metodología: Se han realizado búsquedas en diferentes bases de datos: Scopus, Web Of Science, Pubmed, Science Direct y Google Scholar, sin límite de tiempo hasta junio del 2020. Se identificaron 2783 meta-análisis, de los cuales 44 cumplieron los criterios de inclusión.

Resultados: Entre los factores de riesgo del desarrollo de la EA con una evidencia relativamente fuerte se encuentran: accidente cerebrovascular (n = 2), algunos tipos de colesterol (LDL, TC) (n = 3), depresión (n = 5), diabetes mellitus (n = 7), inactividad física (n = 1), obesidad (índice de masa corporal por encima de 30) (n = 5), algunos tipos de presión arterial elevada (PAS y PA) (n = 3), riesgo cardiovascular (n = 2), tabaquismo (n = 5) y ausencia o incremento de vitaminas (B y D) (n = 3). En algunos estudios no existe evidencia de asociación significativa en los factores de riesgo de: algunos tipos de colesterol (HDL, TG) (n = 2), algunos tipos de presión arterial elevada (PAD) (n = 2), tabaquismo (n = 1), ausencia o incremento de vitaminas (D, B y E) (n = 3)

Conclusión: Si se interviene en los factores modificables que están asociados significativamente con el aumento de la EA, se estima que se podría disminuir la incidencia de esta enfermedad.

Palabras clave: Meta-análisis, Enfermedad de Alzheimer, Factores de Riesgo Modificables.

ABSTRACT

Background: Alzheimer's disease (AD) consists of a neuro-cognitive disorder associated with functional and cognitive loss in people who suffer from it. The identification of factors that can modify the course of AD is essential to be able to intervene on them in order to prevent the disease and/or slow its progression. Therefore, an empirical synthesis of meta-analyses of modifiable factors in AD has been carried out.

Objective: To update and synthesize the empirical evidence provided by meta-analyses on the weight of modifiable risk factors of AD to enable efficient maintenance treatment and improvement of physical and cognitive abilities through non-pharmacological intervention.

Methods: We searched different databases: Scopus, Web Of Science, Pubmed, Science Direct and Google Scholar, with no time limit until June 2020. A total of 2783 meta-analyses were identified, of which 44 met the inclusion criteria.

Results: Risk factors for the development of AD with relatively strong evidence included: stroke (n = 2), some types of cholesterol (LDL, TC) (n = 3), depression (n = 5), diabetes mellitus (n = 7), physical inactivity (n = 1), obesity (body mass index above 30) (n = 5), some types of elevated blood pressure (SBP and BP) (n = 3), cardiovascular risk (n = 2), smoking (n = 5), and lack of or increased vitamins (B and D) (n = 3). In some studies, there is no evidence of significant association in the risk factors of: some types of cholesterol (HDL, TG) (n = 2), some types of elevated blood pressure (DBP) (n = 2), smoking (n = 1), absence or increase of vitamins (D, B and E) (n = 3)

Conclusions: If we intervene in the modifiable factors that are significantly associated with the increase of AD, we can decrease the incidence of this disease.

Keywords: Meta-analysis, Alzheimer's disease, Modifiable Risk Factors.

INTRODUCCIÓN

La EA es un tipo de demencia crónica, irreversible, primaria, con lesiones localizadas en la corteza cerebral y claramente relacionada con la edad. Existe una forma precoz, antes de los 65 años, y una forma tardía, después de los 65 años, que es la más frecuente y que se produce en el 85% de las personas que padecen la EA(21).

La EA es una enfermedad neurodegenerativa primaria, con las propiedades sindrómicas de demencia, que se caracteriza en su forma típica por una pérdida progresiva de la memoria y de una o varias capacidades mentales, con sintomatología clínica tanto a nivel cognitivo como conductual y funcional(22). Los síntomas de la enfermedad fueron identificados por Emil Kraepelin, mientras que la neuropatología característica fue descrita por primera vez por Alois Alzheimer en 1906.

La EA sigue un curso degenerativo progresivo que se caracteriza por un avance insidioso, cuyas manifestaciones sintomatológicas suelen ir apareciendo de manera escalonada. A medida que avanza la enfermedad aparecen diferentes síntomas cognitivos, funcionales y psiquiátricos característicos de la demencia tipo Alzheimer que se establece en diferentes fases(3). Se ha llegado al consenso de establecer tres fases de progresión de la enfermedad (leve, moderada y severa). La progresión de la enfermedad depende de muchos factores, entre los que se incluye la edad del usuario, los cuidados y tratamientos recibidos, el entorno en el que se desarrolla o la existencia de otras patologías que puedan influir en el agravamiento de la EA(4). La duración de la enfermedad puede ir desde un año hasta 15 años.

Los principales signos y síntomas que caracterizan a la EA son: alteraciones cognitivas, de la conducta y neurológicas(6). Dentro de trastornos cognitivos, se podrían incluir problemas de la memoria (el principal síntoma y el más característico de la enfermedad), dificultades del lenguaje, agnosia, apraxia, desorientación y alteración de la función ejecutiva. En el caso de las alteraciones de la conducta se señalan: delirios, alucinaciones, cambios de humor, cambios de la función neurovegetativa y alteraciones de la actividad psicomotora. Con respecto a los signos neurológicos se podrían diferenciar entre: signos extrapiramidales, discinesias, mioclonías, crisis convulsivas, paratonías, alteraciones de la marcha y signos piramidales(1).

Para llegar a entender la repercusión que podría tener la EA en un futuro en nuestro país, es importante tener en cuenta según las proyecciones de población publicadas en la página web del Instituto Nacional de Estadística(23), cuál es el aumento estimado de la población española. En los próximos 15 años, España ganaría 2.375.776 habitantes, hasta superar los 49 millones de personas en el año 2033. La esperanza de vida al nacimiento alcanzaría en el año 2033 los 82,9 años en los hombres y los 87,7 años en las mujeres, respecto a los valores actuales. Se estima que para el año 2030 las personas con demencia en el mundo superen los 80 millones (24), con estos datos, la EA repercutiría en la vida de más de 3,5 millones de personas en nuestro país(24).

La primera causa de muerte en España, en el año 2021, fue la del grupo de enfermedades del sistema circulatorio, seguida de las enfermedades cerebro vasculares y de las enfermedades de cáncer de bronquios y pulmón (24). En este primer grupo de enfermedades circulatorias, las enfermedades isquémicas del corazón y las enfermedades cerebro vasculares ocupan el primer lugar en el número de defunciones, aunque el porcentaje descendió con respecto al año anterior (24). La demencia se sitúa como la quinta causa más frecuente de defunciones en España. La EA se sitúa como la octava causa más frecuente, con un total de 13.045

personas fallecidas; de entre ellas 3.835 fueron hombres y 9.210 fueron mujeres (24). Pero en el último año se destaca el descenso en las defunciones por EA (-16.2%)(24).

Se estima que actualmente, en España, hay cerca de 800.000 personas con EA, más de la mitad en estado de dependencia. Las demencias son el problema sanitario en España que más recursos consume(25). El coste comprende, por un lado, los gastos directos (gasto de consultas médicas, medicación, adaptaciones de la vivienda, ocupación de Centro de día o residencia de ancianos…). Y, por otro lado, los gastos indirectos (cuidadores que dedican muchas horas de su tiempo y que reducen su productividad en el trabajo y requieren una mayor atención médica por sobrecarga, desgaste emocional de la familia, ingreso del enfermo en un centro asistido, coste emocional…)(25).

Actualmente, existen diferentes recursos terapéuticos, farmacológicos y no farmacológicos cuyo objetivo consiste en ralentizar el desarrollo de la enfermedad, mitigar la gravedad de los síntomas y mejorar la calidad de vida de los enfermos y de sus cuidadores(26). Todavía no se dispone de un tratamiento definitivo que sea capaz de detener el curso de la EA. De esta manera se siguen desarrollando investigaciones en este campo para conocer aspectos de la enfermedad que todavía no han sido descubiertos y que en un futuro lograrán determinar cómo abordar y prevenir la enfermedad.

En los últimos años se han realizado muchas revisiones para investigar los distintos factores de riesgo que pueden repercutir en la EA. Algunas de ellas extraen conclusiones contundentes, pero en otras ocasiones, los resultados parecen ser controvertidos. Por esta razón se ha realizado una revisión sistemática extensa y completa de meta-análisis actuales para resumir los principales factores de riesgo modificables de EA. Muchos de estos factores se caracterizan por ser evitables, pudiéndose reducir y controlar mediante intervenciones de prevención primaria dirigidas a la población general y prevención secundaria y terciaria dirigidas a las personas que padecen la enfermedad. Por tanto, el objetivo de este estudio

consiste en actualizar y sintetizar la evidencia empírica aportada por los meta-análisis sobre el peso de los factores de riesgo modificables de la EA para posibilitar un tratamiento de mantenimiento y mejora eficiente de las capacidades físicas y cognitivas a través de la intervención no farmacológica.

METODOLOGÍA

Esta revisión se realizó de acuerdo con la declaración Preferred Reporting for Systematic Reviews and Metaanálisis (PRISMA)(27). Se realizó una búsqueda sistemática en las bases de datos ISI Web of Science (WOS), Scopus, Pubmed, Elsevier Science Direct y Google Scholar. La fecha de corte de la búsqueda fue el 31 de julio de 2020. No se impuso una fecha de inicio de publicación. Se utilizaron combinaciones de los siguientes términos de búsqueda: "presión arterial", "diabetes", "actividad física", "tabaquismo", "vitamina D", "obesidad", "colesterol", "accidente cerebro vascular", "enfermedad coronaria", "depresión" Y "EA" Y "metanálisis". La búsqueda se realizó en inglés y español. Se identificaron 3363 meta-análisis, de los cuales 44 cumplieron los criterios de inclusión.

Los criterios de inclusión que se han determinado en este estudio han sido:

- Criterios de inclusión: 1. Meta-análisis que investigan el efecto de cualquiera de los factores de riesgo modificables en la EA. 2. Que incluyan pacientes con diagnóstico de EA según un criterio de diagnóstico (p. Ej., El Manual diagnóstico y estadístico de trastornos mentales, DSM-III o los criterios de la Asociación del Instituto Nacional de Neurológicos y de la Comunicación-EA y trastornos relacionados, N-ADRDA). 3. Que sean estudios originales revisados por pares que se publican en inglés o en español.
- Criterios de exclusión 1. Revisiones sistemáticas (k = 16). 2. Estudios primarios no publicados como metaanálisis en revistas revisadas por pares (es decir, resúmenes de conferencias, capítulos de libros) (k = 12). 3. Estudios que investigan el efecto de los

distintos factores de riesgo en una población mixta de pacientes con EA y otras demencias (*k* = 23). 4. Estudios donde se investiga el efecto de un fármaco relacionado con un factor de riesgo (*k* = 8). 5. Estudios donde se incluyen factores genéticos (*k* = 13). 6. Estudios que no incluyan un tamaño del efecto (*k* = 5).

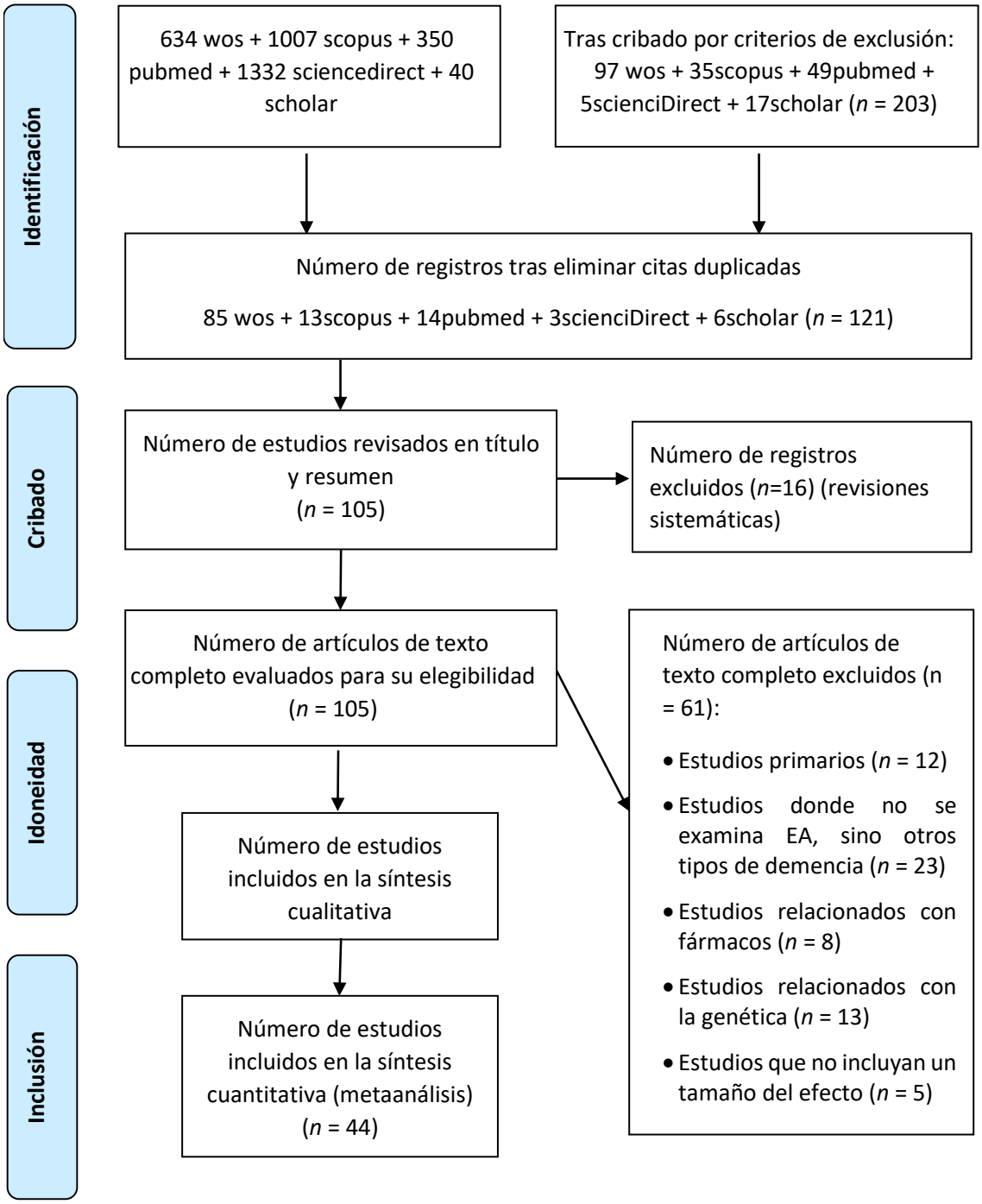

Figura 1. Diagrama de flujo donde se muestra la selección de artículos para el meta-análisis

Para la evaluación de la calidad de los estudios y la extracción de los datos, 3 investigadores expertos realizaron un análisis de manera independiente del título y del resumen. Tras la exclusión de los artículos irrelevantes, todos los meta-análisis restantes se inspeccionaron críticamente para verificar la precisión de los datos. Luego, se revisaron los textos completos de todos los estudios primarios incluidos en cada meta-análisis de acuerdo con los criterios de inclusión. Los datos relacionados con el diagnóstico de EA se obtuvieron directamente del texto o de otras tablas estadísticas de los estudios primarios incluidos.

El autor principal se encargó de extraer de forma independiente los datos correspondientes a cada estudio, incluidas las características del estudio. Los diagnósticos de EA se basaron en criterios clínicos aceptados: Manual diagnóstico y estadístico de trastornos mentales en diferentes ediciones (DSM-III, DSM-III-R, DSM-IV, DSM-V), Clasificación internacional de enfermedades (CIE-10), Criterios revisados y criterios de la Asociación del Instituto Nacional de Trastornos Neurológicos y de la Comunicación-EA y Trastornos Relacionados (N-ADRDA) e Instituto Nacional de Trastornos Neurológicos y de la Comunicación - Asociación Internacional para la Investigación y la Enseñanza en Neurociencias (N-AIREN). Además, la calidad de los informes de los estudios incluidos se evaluó mediante la herramienta Assessment of Multiple Systematic Reviews (AMSTAR)(28), que ha demostrado tener una buena concordancia, fiabilidad y validez de contenido entre evaluadores(28,29).

RESULTADOS

Se han analizado un total de 44 metaanálisis después de revisar títulos, resúmenes y texto completo. Los detalles de cada uno de ellos se encuentran en la Tabla 1.

ACCIDENTE CEREBRO VASCULAR (ACV): En los dos meta-análisis incluidos en la revisión(18,30), la EA se asocia con el ACV con unos valores de *HR* =1.69 (1.49-1.92) y *RR* = 1.13 (0.75-1.70) respectivamente.

COLESTEROL: De los 5 estudios incluidos, tres de los meta-análisis realizados por Zhou et al.(31), Liu et al.(8) y Wu et al.(32). muestran asociación significativa entre las proteínas de baja densidad y los niveles de colesterol total con el riesgo de EA.

DEPRESIÓN: Los resultados de todos los meta-análisis incluidos en esta revisión muestran fuertes asociaciones positivas entre la depresión y la EA con un rango del tamaño del efecto comprendido entre 1.54 y 2.04(33–37).

DIABETES: Los 7 metaanálisis revisados determinan una asociación positiva entre la diabetes y EA. Los valores estadísticos que se muestran en cada estudio oscilan entre los valores de 1.18 a 1.56 (Profenno et al.(38), Cheng et al.(39), Vagelatos et al.(40), Gudala et al.(41), Meng et al.(42), Xu et al.(43), Zhang et al.(44)).

INACTIVIDAD FÍSICA: Los dos meta-análisis encontrados concluyen que existe una asociación positiva entre la inactividad física y el desarrollo de la EA con tamaños del efecto de *HR* =1.36 (1.12-1.65) (Kivimaki et al.(45)) y *RR* = 1.20 (1.02-1.38) (Xu et al.(43)).

OBESIDAD: En todos los metaanálisis revisados, se asocia la obesidad o el índice de masa corporal alto con un mayor riesgo para desarrollar EA. El rango del tamaño del efecto oscila entre 1.35 y 1.88.

PRESIÓN ARTERIAL: Prácticamente en todos los meta-análisis, la presión arterial (PA), a excepción de uno(15), y la presión arterial sistólica (PAS), se asocia positivamente con el riesgo de EA. Los tamaños del efecto oscilan entre *OR* = 1.31 (1.01-1.70) y *RR* = 1.87 (1.36-2.37). Sin embargo, no se encontró asociación entre (presión arterial diastólica) (PAD) y EA(46), *RR* = 0.99 (0.88-1.09).

RIESGO CARDIOVASCULAR: Los dos metaanálisis revisados encontraron una asociación positiva entre el riesgo cardiovascular y la EA cuyos tamaños del efecto varían entre *RR* = 1.07 (0.90-1.28) y *RR* =1.20 (1.02-1.38).

TABAQUISMO: De los seis metaanálisis revisados, cinco de ellos asocian ser fumador con un mayor riesgo de EA(41,42,46-48). Los tamaños del efecto (*RR*) estimaron valores entre 1.37-1.59. En el estudio realizado por Meng et al. se concluye que existe un riesgo doble de desarrollar EA (*HR* = 2.36). Un único metaanálisis concluye que en pacientes fumadores, el tabaquismo actuó como un factor protector de EA *OR* = 0.70 (0.57-0.85)(50).

VITAMINA D: El exceso de vitamina D se asocia con el riesgo de EA, *RR* = 0.93 (0.89,0.97)(51), aunque también la ausencia de vitamina D se asocia con el desarrollo de EA, *HR* = 1.32 (1.16,1.52)(52). Existen otros dos estudios que no encuentran relación entre ausencia de vitamina D y EA, *RR* = 1.55 (0.97,2.49)(53) y *OR* = 1.19 (0.96,1.41)(54). El exceso de Vitamina E no se asocia positivamente con el riesgo de EA, *RR* = 0.81 (0.50-1.33)(55). Además, el exceso de Vitamina B tampoco parece estar vinculado con la EA, *RR* = 0.99 (0.99-1.00)(56).

En síntesis, entre los factores de riesgo del desarrollo de la EA con una evidencia relativamente fuerte se encuentran: accidente cerebrovascular (*n* = 2), algunos tipos de colesterol (LDL, TC) (*n* = 3), depresión (*n* = 5), diabetes mellitus (*n* = 7), inactividad física (*n* = 2), obesidad (índice de masa corporal por encima de 30) (*n* = 4), algunos tipos de presión arterial elevada (PAS y PA) (*n* = 4), riesgo cardiovascular (*n* = 2), tabaquismo (*n* = 5) y ausencia o incremento de vitaminas (B y D) (*n* = 3) (Tabla 1).

En algunos estudios no existe evidencia de asociación significativa en los factores de riesgo de: algunos tipos de colesterol (HDL, TG) (*n* = 2), algunos tipos de presión arterial elevada (PAD) (*n* = 2), tabaquismo (*n* = 1), ausencia o incremento de vitaminas (D, B y E) (*n* = 3) (Tabla 1)

Tabla 1. Meta-análisis extraídos de la búsqueda en las distintas bases de datos.

VARIABLE	AUTORES	AÑO	REGIÓN[1]	Nº ESTUDIOS[2]	MUESTRA[3]	RESULTADO[4]	TAMAÑO DEL EFECTO[5]
ACCIDENTE CEREBRO VASCULAR	Zhou, Jing, Yu et al(30).	2015	EU (3), USA (3)	6	EA *n* = 952 GC *n* = 14730	> ACV > EA	*RR* = 1.13 (0.75,1.70)
	Kuzma, Elzbieta, Lourida, et al(18).	2013	-	19	EA *n* = 237886 GC *n* = 1885536	> ACV > EA	*HR* = 1.69 (1.49,1.92)
COLESTEROL	Zhou, Liang, Zhang et al(31).	2020	EU (7), USA (6), AS (4), AF (2), OC (1)	22	EA *n* = 2266 GC *n* = 4767	> LDL-C > EA	*SMD* = 0.35 (0.12,0.58)
	Liu, Xin, Jiajia et al(8).	2020	EU (3), USA (4), AS (2) EU (4), USA (4), AS (3) EU (6), USA (4), AS (3) EU (4), USA (2)	9	EA *n* = 891 GC *n* = 2399	> LDL-C > EA > TC > EA > HDL-C = EA > TG = EA	*SMD*= 1.40 (0.70,2.10) *SMD* = 0.76 (0.13,1.40) *SMD*= -0.53 (-1.12,0.07) *SMD*= -0.02 (-0.25,0.21)
	Wu, Yufei, Wang et al(32).	2019	AS (33)	33	EA *n* = 3037 GC *n* = 5375	> LDL-C > EA < HDL = EA > TC > EA > TG = EA	*OR* = 1.64 (1.07,2.51) *OR* = 0.81 (0.55,1.19) *OR* = 1.58 (1.10,2.92) *OR* = 1.33 (0.99,1.79)
	Wang, Hua-Long, Wang et al(57).	2016	-	-	EA *n* = 959 GC *n* = 694	> TC = EA	*SMD* = -0.23 (-0.65,0.19)
	Xu, Wei, Tan et al(43).	2015	USA (2), EU (4) USA (8), EU (4), AS (4)	6 16	EA *n* = 12604 GC *n* = 2,256,519	> HDL = EA > TC = EA	*RR* = 1.00 (0.86,1.14) *RR* = 0.96 (0.81,1.11)

VARIABLE	AUTORES	AÑO	REGIÓN[1]	Nº ESTUDIOS[2]	MUESTRA[3]	RESULTADO[4]	TAMAÑO DEL EFECTO[5]
DEPRESIÓN	Kuring, Mathias, Ward et al(34).	2020	-	22	EA *n* = 27084 GC *n* = 55785	> DP > EA	*p* = 0.0001
	Santabarbara, Sevil-Perez, Olaya et al(33).	2019	EU (5), AS (2)	7	EA *n* = 633 GC *n* = 13425	> DP > EA	*RR* = 1.54 (1.05,2.24)
	Cherbuin, Nicolas, Kim et al(35).	2017	EU (19), USA (13), AS (3)	35	EA *n* = 2797 GC *n* = 66532	> DP > EA	*RR* = 2.04 (1.40,2.96)
	Diniz, Breno, Butterset al(36).	2016	-	16	EA *n* = 3437 GC *n* = 20746	> DP > EA	*HR* = 1.54(1.23,1.93)
	Gao, Huang, Zhao et al(37).	2013	EU (1), USA (3)	4	EA *n* = 659 GC *n* = 5686	> DP > EA	*RR* = 1.66 (1.29,2.14)
DIABETES	Zhang, Chen, Chunxiang et al(44).	2018	-	-	EA *n* = 710858 GC *n* = 1035919	> D > EA	*RR* = 1.53 (1.42,1.63)
	Xu, Tan, Lan et al(43).	2015	-	34	*N* = 188515	> D > EA	*RR* = 1.18 (1.07,1.29)
	Meng, Yu, Wang et al(42).	2014	EU (2), AS (3)	5	EA *n* = 529 GC *n* = 8971	> D > EA	*OR* = 1.4 (1.25,1.57)
	Gudala, Bansal, Schifano et al(41).	2013	EU (8), USA (15), AS (6)	29	EA *n* = 91052 GC *n* = 1148767	> D > EA	*RR* = 1.56 (1.41,1.73)
	Vagelatos, Eslick, Guy et al(40).	2013	EU (6), USA (5), AS (5)	16	EA *n* = 12321 GC *n* = 2122883	> D > EA	*OR* = 1.55 (1.4,1.73)

VARIABLE	AUTORES	AÑO	REGIÓN[1]	Nº ESTUDIOS[2]	MUESTRA[3]	RESULTADO[4]	TAMAÑO DEL EFECTO[5]
	Cheng, Huang, Deng et al(58).	2012	EU (5), USA (11), AS (1)	17	EA *n* = 5761 GC *n* = 42434	> D > EA	*RR* = 1.46 (1.2,1.77)
	Profenno, Porsteinsson, Faraonea et al(38).	2010	EU (9), USA (1)	10	EA *n* = 1750 GC *n* = 23416	> D > EA	*RR* = 1.54 (1.33,1.79)
INACTIVIDAD FÍSICA	Kivimaki, Singh-Manoux, Pentti et al(45).	2019	-	11	EA *n* = 1604 GC *n* = 354143	> IA > EA	*HR* = 1.36 (1.12,1.65)
	Xu, Wei, Tan et al(43).	2015	-	10	*N* = 5524	> O > EA	*RR* = 1.20 (1.02,1.38)
OBESIDAD	Meng, Yu, Wang et al(42).	2014	EU (4), USA (3), AS (2)	9	EA *n* = 1041 GC *n* = 13786	> O > EA	*OR* = 1.88 (1.32,2.69)
	Beydoun, Beydoun, Wang et al(47).	2014	EU (1), USA (4)	5	EA *n* = 802 GC *n* = 25964	> O > EA	*OR* = 1.81 (1.00,3.29)
	Anstey, Cherbuin, Budge et al(59).	2011	USA (7)	7	EA *n* = 13166 GC *n* = 15256	> O > EA	*RR* = 1.35 (1.19,1.54)
	Profenno, Porsteinsson, Faraonea et al(38).	2010	EU (6), USA (4), AS (1)	11	EA *n* = 928 GC *n* = 18064	> O > EA	*HR* = 1.59 (1.02,2.48)

VARIABLE	AUTORES	AÑO	REGIÓN[1]	Nº ESTUDIOS[2]	MUESTRA[3]	RESULTADO[4]	TAMAÑO DEL EFECTO[5]
PRESIÓN ARTERIAL	Lennon, Makkar, Crawford et al(60).	2019	EU (2), USA (2), AS (3)	7	EA *n* = 2591 GC *n* = 877321	> PA > EA	*HR* = 1.25 (1.06,1.47)
	Wang, Xu, Wang et al(46).	2018	EU (2), USA (2), AS (3)	7	EA *n* = 2468 GC *n* = 876653	> PAS > EA > PAD = EA	PAS: *HR* = 1.4 (1.1,1.8)
	Xu, Wei, Tan et al(43).	2015	-	49	*N* = 2290617	> PAS > EA > PAD = EA	*RR* = 1.87 (1.36,2.37) *RR* = 0.99 (0.88,1.09)
	Meng, Yu, Wang et al(42).	2014	EU (3), USA (3), AS (1)	7	EA *n* = 529 GC *n* = 8971	> PA > EA	*OR* = 1.31(1.01,1.70)
	Guan, Huang, Li et al(15).	2011	EU (2), USA (7)	9	EA *n* = 7982 GC *n* = 15146	> PA = EA	*RR* = 1.01 (0.87,1.18)
RIESGO CARDIOVASCULAR	Wolters, Segufa, Darweesh, Sirwan et al(61).	2018	EU (4), USA (3), OC (1)	8	EA *n* = 18715 GC *n* = 1309483	> RC > EA	*RR* = 1.07 (0.90,1.28)
	Xu, Wei, Tan et al(43).	2015	-	2	*N* = 7011	> RC > EA	*RR* = 1.20 (1.02,1.38)
TABAQUISMO	Xu, Wei, Tan et al(43).	2015	-	4	*N* = 16028	> T > EA	*RR* = 1.96 (1.37,2.54)
	Zhong, Wang, Zhang et al(48).	2015	-	-	EA *n* = 5787 GC *n* = 919549	> T > EA	*RR* = 1.40 (1.13,1.73)
	Beydoun, Beydoun, Wang et al(47).	2014	EU (15), USA (11), AS (5), OC (1)	32	*N* = 170816	> T > EA	*RR* = 1.37 (1.23,1.52)

VARIABLE	AUTORES	AÑO	REGIÓN[1]	Nº ESTUDIOS[2]	MUESTRA[3]	RESULTADO[4]	TAMAÑO DEL EFECTO[5]
VITAMINAS	Meng, Yu, Wang et al(42).	2014	EU (2), USA (1), AS (2)	5	EA *n* = 961 GC *n* = 14688	> T > EA	*HR* = 2.36 (1.54,3.61)
	Peters, Poulter, Warner et al(49).	2008	EU (3), USA (3), AS (1)	7	-	> T > EA	*OR* = 1.59 (1.15,2.20)
	Fontelles, Carvalho, D'Oliveira(50)	2007	-		EA *n* = 1544 GC *n* = 3962	> T < EA	*OR* = 0.70 (0.57,0.85)
	Bingyan, Fulin, Wu et al(52).	2019	EU (3), USA (13)	16	*N* = 14618	< VIT D > EA	*HR* = 1.32 (1.16,1.52)
	Kui, Chen, Xiaoguang et al(53).	2019	EU (5), USA (1)	6	EA *n* = 1607 GC *n* = 21692	> VIT D = EA	*RR* = 1.55 (0.97,2.49)
	Wang, Li, Zhang et al(55).	2019	USA (5)	5	EA *n* = 244 GC *n* = 14262	> VIT E = EA	*RR* = 0.81 (0.50,1.33)
	Ahmad, Ali, Shab-Bidar(54)	2019	EU (5), USA (3)	8	EA *n* = 1607 GC *n* = 28354	> VIT D < EA	*OR* = 1.19 (0.96,1.41)
	Chen, Xue, Li et al(51).	2018	EU (7), USA (3)	10	*N* = 28640	> VIT D > EA	*RR* = 0.93 (0.89,0.97)
	Doets, van Wijngaarden, Szczecinska et al(56).	2011	-	-	EA *n* = 431 GC *n* = 9415	> VIT B = EA	*RR* = 0.99 (0.99,1.00)

Notas:
[1]Región: *N*: número de estudios independientes. AF (África); AS (Asia); EU (Unión Europea); OC (Oceanía); USA (Estados Unidos)
[2]*N*: Número de estudios primarios que conforman el metaanálisis
[3]Muestra: EA_n (Número de personas con Enfermedad de Alzheimer); GC_n (Número de personas del Grupo control); *N* (Número total de la muestra)
[4]Resultado: ACV: Accidente Cerebro Vascular; LDL-C: Nivel de lipoproteínas de baja densidad; HDL-C: Nivel de proteínas de alta densidad; TC: Colesterol total; TG: Triglicéridos; DP: Depresión; D: Diabetes; IA: Inactividad física; O: Obesidad; PA: Presión Arterial; PAS: Presión Arterial Sistólica; PAD: Presión Arterial Diastólica; RC: Riesgo Cardiovascular; T: Tabaco; Vit: Vitaminas; EA: Enfermedad de Alzheimer.
[5]Tamaño del efecto: HR: Hazard Ratio; OR: Odds Ratio; RR: Risk Ratio; SMD: Standard Mean Difference

DISCUSIÓN

Los resultados de esta revisión sistemática de meta-análisis han logrado el objetivo de analizar los distintos factores de riesgo modificables de la EA. Este estudio muestra, por tanto, la relación de distintos factores de riesgo (accidente cerebro vascular, algunos tipos de colesterol, depresión, diabetes, inactividad física, obesidad, algunos tipos de presión arterial, factores de riesgo cardiovascular, tabaco y algunos déficits o excesos de vitaminas) con la EA para aportar un conocimiento más preciso sobre esta enfermedad de alta prevalencia en nuestro país.

ACCIDENTE CEREBRO-VASCULAR: En nuestra revisión, existe unanimidad de que los ACV está asociados a la EA. Una de las razones que se argumentan sobre la relación entre EA y el ACV es que ambas enfermedades afectan al cerebro y el ACV puede acelerar la degeneración cerebral que se presenta en la EA(30).

COLESTEROL: No existe un consenso claro sobre la relación entre colesterol y EA. Solo tres meta-análisis aportan evidencias empíricas sobre esta asociación(8,31,32). Sin embargo, no se encuentran diferencias significativas entre la asociación de triglicéridos y el nivel de proteínas de alta densidad con la EA en tres de los meta-análisis revisados(8,32,43). La teoría de las placas seniles podría explicar la relación entre el LDL-C, TC y EA, al plantear que el depósito extracelular de proteína amiloide (A) dificulta las conexiones sinápticas neuronales en el cerebro y aumenta el riesgo de EA(62,63).

DEPRESIÓN: Los datos de los meta-análisis revisados en este estudio sobre la asociación entre depresión y EA son muy robustos. Una de las hipótesis que puede explicar esta asociación es el uso de medicamentos anticolinérgicos, que se utilizan para el tratamiento de la depresión y que, por su efecto en el organismo, están asociados con un incremento del riesgo de demencia(64–67).

DIABETES: Tal y como muestra esta revisión, la diabetes mellitus tipo 2 (DM2), como se sospechaba desde hace mucho tiempo, se presenta como un factor de riesgo para la EA(40). La DM está asociada con cambios cognitivos y existen varios estudios que incluso relacionan el mecanismo de la resistencia a la insulina y la patogénesis de la formación de placa y la señalización neuronal alterada en la EA(41). A pesar de la unanimidad de los resultados encontrado, hoy en día, la asociación entre la diabetes y la demencia siguen siendo un área de controversia(44).

INACTIVIDAD FÍSICA: Esta revisión concluye que existe una relación entre las personas que son físicamente inactivas y la EA. La relación que existe entre inactividad física y ciertas enfermedades, como por ejemplo la diabetes, la enfermedad cardiaca coronaria y el accidente cerebrovascular(45), que se encuentran asociadas a EA, podría explicar que fuera un factor de riesgo de esta enfermedad neurodegenerativa.

OBESIDAD: Como en todos los meta-análisis revisados, la mayoría de estudios epidemiológicos que abordan el sobrepeso/obesidad, sugieren que existe una asociación entre la obesidad y la EA, especialmente en estudios donde existe un periodo de seguimiento mayor(68). La relación entre ambos factores puede deberse a que la obesidad se relaciona con otras enfermedades cardiovasculares y otras patologías como trastornos neurocognitivos, resistencia a la insulina, hipertensión(69), que son a su vez factores de riesgo de la EA(68). Por lo tanto, tener sobrepeso incidiría directa e indirectamente en el desarrollo de la EA a largo plazo.

PRESIÓN ARTERIAL: Tras la revisión de los metaanálisis, se puede concluir que la presión arterial (PA) y la presión arterial sistólica (PAS), excepto en un caso, se asocia positivamente con el riesgo de EA. La relación de la presión arterial con la EA es todavía un misterio. Existe mucha controversia en la literatura científica acerca de la relación entre estos dos factores. Algunos estudios muestran que las demencias vasculares se asocian con la

hipertensión(15). Las razones podrían derivarse de la presión arterial que se puede generar en el cerebro y que podría desembocar en una demencia a largo plazo.

RIESGO CARDIO-VASCULAR: Este estudio arroja evidencia empírica unánime sobre la asociación entre el riesgo cardiovascular y la EA. Existen muchos estudios como el de Ford(10) en el que la mayoría de los factores de riesgo cardiovasculares muestran una relación positiva con la EA. Las enfermedades del corazón y del cerebro coexisten en las personas mayores. Wolters et al.(61) sugieren que el corazón y el cerebro están vinculados de tal forma que, al ser diagnosticado con una enfermedad vascular, el sujeto está predispuesto a desarrollar una demencia.

TABAQUISMO: Este estudio arroja una amplia evidencia sobre el tabaquismo como factor de riesgo de desarrollar EA. Hoy en día, nadie cuestiona que fumar perjudica la salud gravemente. Además de los riesgos bien conocidos como el cáncer de pulmón, fumar también es un predictor independiente de morbilidad cardiovascular, desarrollo de infarto de miocardio y mortalidad, además de acelerar la atrofia cerebral, el declive perfusional y las lesiones de la sustancia blanca(48). El tabaquismo aumenta el riesgo de EA y puede aumentar el riesgo de otras demencias, esto refuerza la necesidad de dejar de fumar, especialmente a partir de los 65 años(49).

VITAMINA D: En este estudio la variabilidad sobre los resultados obtenidos en cuanto al déficit o exceso de Vitamina D su relación con EA es alta. La vitamina D juega un papel importante en la neurotrofia, neurotransmisión, neuroprotección y neuroplasticidad y se ha sugerido que la deficiencia de vitamina D puede desempeñar un factor clave en la progresión de la demencia y la EA(52). Los organismos obtienen principalmente vitamina D a través de la ingesta de alimentos y la síntesis de la piel(52). La vitamina D es crucial para mantener la función cognitiva en la personas mayores, estos receptores de vitamina D están presentes en algunas regiones del cerebro que son responsables del correcto funcionamiento de la

memoria y las funciones cognitivas; aunque no se haya alcanzado un consenso global del valor óptimo para la vitamina D en el cuerpo humano(52).

La revisión de los 44 metaanálisis seleccionados aporta resultados muy robustos sobre la relación que existe entre 7 de los factores de riesgo modificables (accidente cerebro vascular, colesterol LDL-C, depresión, diabetes, inactividad física, obesidad, tipos de presión arterial sistólica, factores de riesgo cardiovascular y tabaco) y la EA. A pesar de los hallazgos encontrados en esta revisión de meta-análisis, existen una serie de limitaciones que se deben considerar. En primer lugar, en algunos de los estudios no se conoce la muestra o ésta es demasiado pequeña, por lo que no serían representativas de la población. En segundo lugar, la representatividad de regiones como África y Oceanía es insuficiente. En tercer lugar, la búsqueda se limitó a dos idiomas: inglés y español. Por último, los metaanálisis estaban compuestos de estudios longitudinales y transversales, lo que dificultad extraer conclusiones sobre la causalidad de estos factores sobre la EA. Sería conveniente seleccionar solo los estudios longitudinales de cada metaanálisis con seguimiento a largo plazo para poder obtener resultados más concluyentes sobre el posible efecto causal que puedan tener estos factores modificables sobre el desarrollo de la EA.

Se considera que las terapias no farmacológicas y la adopción de algunos estilos de vida pueden ser protectores frente a estas enfermedades neurológicas que afectan multifactorialmente a la población. En este sentido, la Terapia Ocupacional se consolida como una de las disciplinas cuyo objetivo se centraría en mejorar el desempeño de las actividades de la vida diaria y aumentar el rendimiento cognitivo y emocional mediante programas de intervención donde se puedan incluir ejercicios para la movilidad funcional, de estimulación cognitiva y sensorial y rehabilitación de funciones cognitivas como la memoria (afectada principalmente en la EA)(70,71). En el estudio realizado por Matilla-Mora et al.(70) se demostró la eficacia y efectividad de la Terapia Ocupacional en el retraso de la progresión

de las distintas disfunciones en personas con EA. La variabilidad de intervenciones que se disponen en Terapia Ocupacional es amplia, por lo que la intervención a distintos niveles de atención será fundamental. En prevención primaria, la mitad de los casos se pueden prevenir mediante el control de los factores de riesgo y la promoción de estilos de vida saludables(72), por lo tanto, se podría tratar de forma anticipada todos aquellos factores considerados de riesgo y procurar la detección precoz de enfermedades. La prevención secundaria es esencial para limitar su progresión y favorecer su independencia(73). En este sentido, se puede realizar una adaptación del entorno que favorezca los desplazamientos y estimule el mantenimiento de la independencia(74). En la prevención terciaria se incluiría el tratamiento de las complicaciones derivadas de la enfermedad. La Terapia Ocupacional tendría como objetivos la reducción y modulación de síntomas y la optimización de aspectos relacionados con la calidad de vida de la persona con demencia y su cuidador familiar(75). En síntesis, se debería incidir en la existencia de hábitos relacionados con el estilo de vida que actúan como factores de riesgo y hábitos protectores para el desarrollo de EA(76).

CONCLUSIÓN

En este estudio se ha realizado una revisión sistemática de 44 meta-análisis en el que se tiene en cuenta la gran mayoría de los factores de riesgo modificables que influyen en la aparición de EA. Se han analizado los distintos factores de riesgo de la EA y se ha visto la complejidad de su etiología y la controversia literaria que existe sobre algunos de ellos. Sin embargo, los resultados son más controvertidos sobre los tipos de colesterol (HDL-C, TG y TC), presión arterial diastólica y vitaminas que sí están asociados a la EA.

En esta tesis, los factores de riesgo de EA que se han seleccionado para analizarlos de una forma más profunda con técnicas meta-meta-analíticas son: colesterol, depresión, hipertención arterial e ictus. Las razones para analizar estos factores de riesgo de manera específica es la relación tan fuerte que existe entre ellos y la EA(20,77). Por una parte,

colesterol, hipertensión arterial e ictus son considerados como factores de riesgo cardiovascular y se han asociado con la EA(78). En la fisiopatología de la EA se forman placas y ovillos neurofibrilares que se acumulan en el cerebro y que las patologías vasculares aumentan la formación de las mismas, lo que puede explicar su vinculación con la EA(79). Por otra parte, la depresión es una de las complicaciones psiquiátricas más frecuentes de la EA y afecta hasta al 50% de los pacientes(80). Además, la depresión se asocia con una peor calidad de vida, mayor discapacidad en las actividades de la vida diaria, un deterioro cognitivo más rápido, una alta tasa de ingreso en hogares de ancianos, mortalidad relativamente más alta y una mayor frecuencia de depresión y sobrecarga en los cuidadores(81). Por todos estos motivos se han realizado meta-análisis de la relación de estos factores de riesgo modificables (colesterol, depresión, hipertención arterial e ictus) con la EA.

CAPÍTULO 2

"No sé quién soy y no sé qué será lo siguiente que pierda."

Julianne Moore

Sáiz-Vazquez O, Puente-Martínez A, Ubillos-Landa S, Pacheco-Bonrostro J, Santabárbara J. Cholesterol and Alzheimer's disease risk: a meta-meta-analysis. Brain sciences. 2020; 10(6): 386. Doi:10.3390/brainsci10060386

CAPÍTULO 2: CHOLESTEROL AND ALZHEIMER'S DISEASE RISK: A META-META-ANALYSIS

ABSTRACT

Background: Alzheimer 's disease (AD) is the most common subtype of dementia. In the last ten years, the relationship between cholesterol and AD has been investigated. Evidence suggests that cholesterol is associated with AD and represents promising targets for intervention. However, the causality of these associations is unclear. Therefore, we sought to conduct a meta-meta-analysis to determine the effect of cholesterol on the development AD. Then, we assessed the effect of serum levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC) and triglycerides (TG), on AD risk.

Methods: A systematic search of meta-analyses was conducted. Scopus, Web of Science, Science direct, PubMed and Google academic system databases were reviewed.

Results: We found 100 primary studies and five meta-analyses to analyze the relationships between cholesterol and AD. The total effect of cholesterol on risk of AD was significant and heterogeneous. Subgroup analysis shows that LDL-C levels influence the development of AD. However, non-significant effects of HDL-C, TC and TG levels on AD were found.

Conclusions: These results strengthen the evidence that LDL-C cholesterol levels increase risk for AD. More initiatives to investigate the relationship between cholesterol and AD are needed.

Keywords: Alzheimer 's disease; etiology; cholesterol; risk factors; meta-analysis

INTRODUCTION

Alzheimer 's disease (AD) is the most common neurodegenerative disorder resulting in cognitive impairment. AD is characterized by a gradual decline in memory and other cognitive and executive functions, and the progressive development of affective and behavioral disorders (8). The onset of AD is insidious, and its progression is gradual. As it progresses, various patterns of deficits are seen, but the disorder most commonly begins with deficits in recent memory, which are followed by aphasia, apraxia and agnosia after several years (3). AD also may cause psychiatric symptoms and personality changes (82). At the beginning, it affects some abilities, but in the most severe stages, people may depend entirely on others for basic activities of daily living (3).

The etiology of AD is unknown (83). With the global population aging, AD has increased considerably and become a primary concern for governments and the scientific and medical communities (84). In Europe, the AD rate is around 5.05% (3.31% for men and 7.13% for women). The AD increase by age reaches 4% of prevalence worldwide, and it increases to 4.02% in people over 60 years old (85,86). A recent study indicated that the prevalence of AD in individuals aged 60 to 69 years was 1.9 times higher in females than in males (108 cases versus 56 cases per 10,000 persons) (86). In Spain, around 400,000 people suffer from AD, with the highest prevalence in central and north-eastern Spain (87).

Disorders of lipid homeostasis are common risk factors for cardiovascular disease, which is linked to AD (88). Dyslipidemia has been identified as a risk factor for AD (8). This concept refers to abnormal levels of lipids or lipoproteins in the blood, which include high levels of low-density lipoprotein (LDL-C), low levels of high-density lipoprotein (HDL-C), total cholesterol (TC) and triglycerides (TG) (8). According to previous results, the overall performance of four independent test results should be considered indexes for the prediction

of AD, and provide accurate information on an individual's lipid metabolism status or serum lipid and cholesterol levels (32,89,90).

In the last ten years, the relationship between cholesterol and AD has been extensively investigated, especially in longitudinal epidemiological studies (89). Evidence suggests that there is a relationship between having high cholesterol levels in blood in mid- and late-life and the development of dementia (8,43). Specifically, some studies have demonstrated that dyslipidemia, mainly a high level of LDL-C, has vascular and neurotoxic effects, and is implicated in the pathogenesis of AD (89,91–93). Additionally, another study indicates that if the TC in the brain membrane increases, synapses are not performed normally and, therefore, affect cognitive degeneration in AD (94). Nevertheless, other studies did not find an association between hypercholesterolemia (high levels of LDL-C, TC, and TG) and AD (57,95). Regarding HDL-C levels, Tynkkynen et al. found that high levels of HDL-C were inversely associated with the risk of AD. Other studies share the same finding (96,97). However, some studies did not find an association between high triglycerides levels and high levels of HDL-Cproteins and AD (8,32,57).

The study of the disorders of lipid homeostasis is essential, because it may reduce the consequences of vascular diseases and neurodegenerative diseases, among others, in a cost-effective way (8). First, this study aimed to conduct a meta-meta-analysis to determine the global effect of cholesterol on AD risk. Second, as there was no consensus in the previous literature about the impact of different types of cholesterol on AD, the effects of serum levels of LDL-C, HDL-C, TCTG on the development of AD were analyzed.

MATERIALS AND METHODS

I. Data Collection

We applied the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses (27). For data collection, we searched meta-analyses reporting outcomes in individuals with diagnoses of AD. To locate potentially suitable studies, we conducted several searches using 5 electronic databases (last search completed in January 2020), including the Web of Science, Scopus, Pubmed, Science Direct and Google Scholar. No publication date was imposed. The electronic search adopted several combinations of the following keywords: "cholesterol" AND Alzheimer 's disease AND meta-analysis. The same search strategy was used in academic Google but limited to the title. Articles were also searched manually and, if required and when feasible, authors were contacted directly for additional information. The search was also done in the Spanish language.

The study selection included previous meta-analyses that met the following criteria: (1) meta-analysis studies that included measures for cholesterol (LDL-C, HDL-C, TC and TG) and AD diagnosis; (2) they should be written in English or Spanish; (3) quantitative studies that reported effect sizes or data that enabled effect size calculation or estimation; (4) meta-analyses that included human samples.

All abstracts were independently analyzed by 2 researchers. Then, after the exclusion of irrelevant abstracts, all remaining articles were critically inspected to check data accuracy. For meta-analyses that met the inclusion criteria, a third investigator independently extracted the salient data. Data were collected directly from the text, correlation matrixes or other statistical tables from the included studies (Appendix 2: table A1).

The primary variable (type of cholesterol), design (cross-sectional or longitudinal studies), country of origin of the study, sample size, gender, mean age, main results and an effect size

of the relationships between cholesterol and AD were extracted. Information on all the collected data from the selected studies is presented in Table 2.

II. Quality Assessment

Quality of the meta-analyses was independently coded by two co-authors using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) tool (28), which has shown to have good inter-rater agreement, reliability, and content validity (28,29).Total scores for each meta-analysis were calculated as the sum of the 11 items on a binary scale. Quality classifications were established as low quality (0–4), moderate quality (5–8), and high quality (9–11).

III. Statistical Analysis

We conducted meta-meta-analysis, combining standard mean difference (*SMD*), odds ratio *(OR*), and risk ratio (*RR*) for AD reported in the selected meta-analyses (98). We report separate meta-analytic results for each meta-analysis in Table 1. Additionally, we identified separate effect sizes for LDL-C, HDL-C, TC and TG cholesterol levels and their relationship with AD risk. The most frequently reported measure of the associations with cholesterol was *SMD* and *OR*. Hence, the results of this meta-meta-analysis are reported in *OR* format. For each meta-analysis, we calculated (see Tables 3–6): (a) the 95% confidence interval of the effect; (b) the *Z*-value and *p* (two-tailed significance); and (c) *k* or number of studies (99). *RRs* and *ORs* were considered as equivalent, as deemed appropriate when the outcome condition is relatively rare (incidence < 15%) (100). Adjusted effect measures were used in the analysis when they were included in the source studies, under the assumption that adjustment was performed to remove bias in the estimate of the association between cholesterol and AD. We conducted a random-effect model that allowed *SMD* and *ORs* to be incorporated into the same input. Random-effect models are more appropriate than fixed-effect models when the number of studies included in the meta-analysis is low (< 10) (101).

Initially, we performed an analysis summarizing all the available data into a single pooled estimate (102). Then, to assess the heterogeneity of our results, subgroup analyses were performed to examine the differential effects of type of cholesterol: (1) LDL-C, (2) HDL-C, (3) TC and (4) TG. We did not assume a common among-study variance component across subgroups.

We calculated summary estimates and plotted the effects, using Comprehensive Meta-Analysis software (103). The heterogeneity of the results obtained from the different meta-analysis was calculated using the Q statistic. Additionally, the presence of heterogeneity was evaluated by calculating the I^2. The I^2 statistic explains the percentage of variance in the observed effects due to variance in the true effects. I^2 values of 25% are considered as low-heterogeneity, 50% as moderate-heterogeneity, and 75% as high-heterogeneity (102). Statistical significance was set at $p \leq 0.05$. The effect sizes of the mean differences were estimated using Cohen's criteria (104). A small effect was conceptualized as $d = 0.20$, medium $d = 0.50$, and large $d = 0.80$.

Regarding the risk of AD and the cholesterol component, the direction of the reported effect size coefficient was reversed wherever necessary, such that all included effect sizes represented the association between cholesterol and an increase in the risk of suffering from AD, instead of a decrease in the AD risk.

RESULTS

A total of 331 studies were identified from major databases: 64 in ISI Web of Science (WOS), 141 in Scopus, 45 in PubMed, 79 in the Elsevier Science Direct and two in Google Scholar. Twenty-two meta-analyses were eligible for inclusion in this meta-meta-analysis. Of these, 17 were excluded because: (a) $k = 2$ did not report an effect size; (b) $k = 2$ did not provide information on the relationship between cholesterol and AD; (c) $k = 6$ were duplicated; (d) $k = 5$ were systematic reviews about other issues; (e) $k = 1$ aimed to study the effect of

medication on AD; and (f) one meta-analysis that included the same primary studies as another study (see Figure 2). Finally, a total of $K = 5$ meta-analyses were analyzed in this meta-meta-analysis ($k = 12$ pooled effect sizes), including data from $n = 100$ primary studies ($n = 236$ effect sizes).

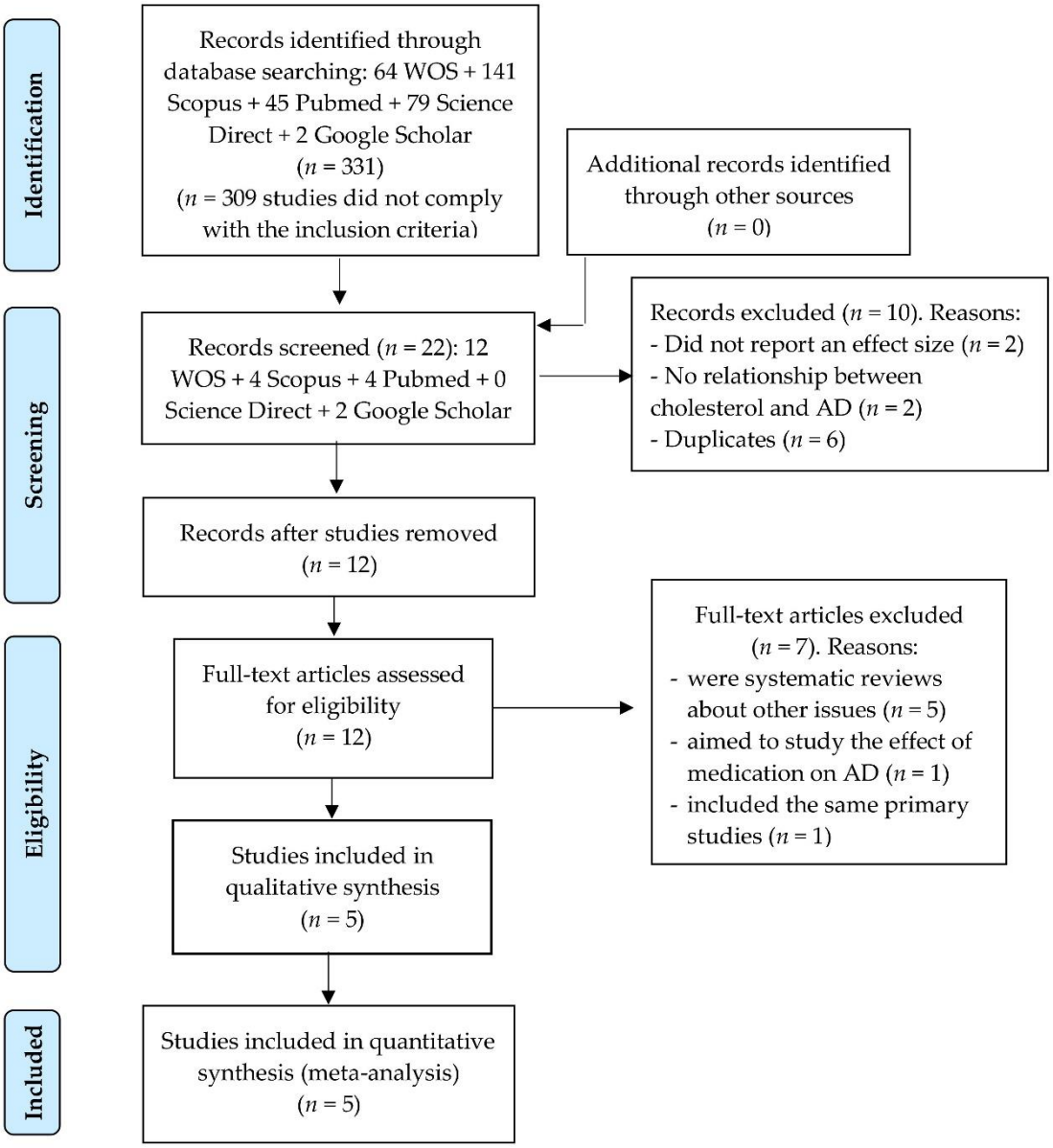

Figura 2. Flow chart depicting the selection of articles for our meta-meta-analysis. Note: AD: alzheimer's disease; n: number of studies

.

Tabla 2. Population characteristics in studies of Alzheimer's Disease (AD) and cholesterol.

Study	Variable	Total *n*	Design	*K*	Country (*N*)	Sample	% F	Age	Result	Effect Size	95% *CI* LL~UL	*p*	AMSTAR
Zhou et al. (31)	LDL-C	AD *n* = 2266 HC *n* = 4767	C	20	EU (7), USA (6), AS (4), AF (2), OC (1)	AD *n* = 2266 HC *n* = 4767	69.50	50-87	> LDL-C > AD	*SMD* = 0.35	0.12~0.58	<0.01	10
Liu et al. (8)	LDL-C	AD *n* = 891 HC *n* = 2399	C	9	EU (3), USA (4), AS (2)	AD *n* = 584 HC *n* = 2130	70	59-92	> LDL-C > AD	SMD = 1.40	0.70~2.10	0.000	11
	HDL-C			11	EU (4), USA (4), AS (3)	AD *n* = 727 HC *n* = 2233			HDL-C = AD	*SMD* = −0.53	−1.12~0.07	0.082	
	TC			13	EU (6), USA (4), AS (3)	AD *n* = 809 HC *n* = 2303			> TC > AD	*SMD* = 0.76	0.13~1.40	0.019	
	TG			6	EU (4), USA (2)	AD *n* = 273 HC *n* = 239			> TG = AD ns.	*SMD* = −0.02	−0.25~0.21	0.859	
Wu et al. (32)	LDL-C	AD *n* = 3037 HC *n* = 5375	C	33	AS (33)	AD *n* = 2843 HC *n* = 5174	53.87	56–84	> LDL-C > AD	*OR* = 1.64	1.07~2.51		10
	HDL-C			33		AD *n* = 2921 HC *n* = 5271			< HDL = AD ns.	*OR* = 0.81	0.55~1.19		
	TC			33		AD *n* = 2661 HC *n* = 5189			> TC > AD	*OR* = 1.58	1.10~2.92		
	TG			28		AD *n* = 2556 HC *n* = 4903			> TG = AD ns.	*OR* = 1.33	0.99~1.79		
Wang et al. (57)	TC	AD *n* = 959 HC *n* = 694	C	16	-	AD *n* = 959 HC *n* = 694	60.21	60–94, *M* = 71.38	> TC = AD	*SMD* = −0.23	0.65~0.19	0.29	10
Xu et al. (43)	HDL-C	AD *n* = 12604 HC *n*=2,256,519	L(2–9)	6	USA (2), EU (4)	AD *n* = 499 HC *n* = 11,991	56.3	*M* = 71.21	> HDL = AD	*RR* = 1.00	0.86~1.14	0.942	11
	TC		L (3.2–32)	16	USA (8), EU (4), AS (4)	AD *n* = 12275 HC *n* = 2,246,750	49.5	*M* = 68.5	> TC = AD	*RR* = 0.96	0.81–1.11	0.000	

Note: Variables: AD: Alzheimer's disease; LDL-C: Low-Density Level Cholesterol; HDL-C: High-Density Level Cholesterol; TC: Total Cholesterol; TG: Triglycerides; Total *n*: number of participants of each study; Design: C: Cross-sectional; L: Longitudinal (year); *K*: Number of Studies; Country *N*: Number of Independent Studies in of each country. EU: European Union; USA: United States of America; AS: Asia; AF: Africa; OC: Oceania; [6]Independent Sample: AD: Alzheimer´s Disease cases; HC: Healthy Control participants for each type of cholesterol.; F: females; M: Mean; *CI*: 95% Confidence Interval; LL: Lower Limit; UL: Upper Llimit; *SMD*: Standard Mean Difference; *OR*: Odds Ratio; *RR*: Risk Ratio; AMSTAR: AMSTAR Score.

Table A1 (Appendix 2) show the available primary studies of cholesterol and AD (K = 100 studies) and the main characteristics. It is worth noting that the search for suitable meta-analyses was systematic. To carry out the main analysis, cholesterol studies were divided into groups based on the type of lipid serum at which cholesterol was placed in each meta-analysis: LDL-C, HDL-C, TC, and TG. Table A2 (Appendix 2) illustrates the individual effect sizes obtained from the meta-analysis of the 100 primary studies to facilitate the replicability of this study and further analysis.

Twelve effect sizes were extracted from a total of five meta-analyses. K = 3 effect sizes informed about LDL-C and risk of AD (25%); k = 3 about HDL-C (25%); k = 4 about TC (33.3%), and k = 2 of TG (16.7%). Table 2 summarizes the key features of the included primary diagnosis, design, number of primary studies, country of origin of the study, sample size, gender, mean age, results, total scores of quality of included meta-analyses (MAs) (AMSTAR) and effect sizes of the relationships between cholesterol and AD that were extracted.

First, we investigated the relationship between overall cholesterol components and risk of AD in five meta-analyses, with a total of 2,289,511 participants, most of whom were female (N cases, AD = 19,757; N controls, HCs = 2,269,754). We identified a total of 12 estimates for cholesterol serum lipids (LDL-C, HDL-C, TC, and TG). The distribution of these estimates is shown in Figure 3.

The total random effect of cholesterol on risk of AD was significant with OR = 1.29, 95% confidence interval (CI) [1.04, 1.60], Z = 2.28, p = 0.023, d = 0.14. When calculating the overall effect of lipid parameters, evidence of significant heterogeneity was found (Q = 45.49, df = 11, p = 0.0001, I^2 = 75.82%). Therefore, we examined whether subgroup analysis changed the results, as cholesterol levels at onset were significantly associated with AD. Heterogeneity could be explained, due to the different types of cholesterol: LDL-C, HDL-

C, TG and TC. The results indicated that there were differences between the types of cholesterol: $Qb = 9.04$, $df = 3$, $p = 0.029$. Hence, independent analyses for each type of cholesterol were performed.

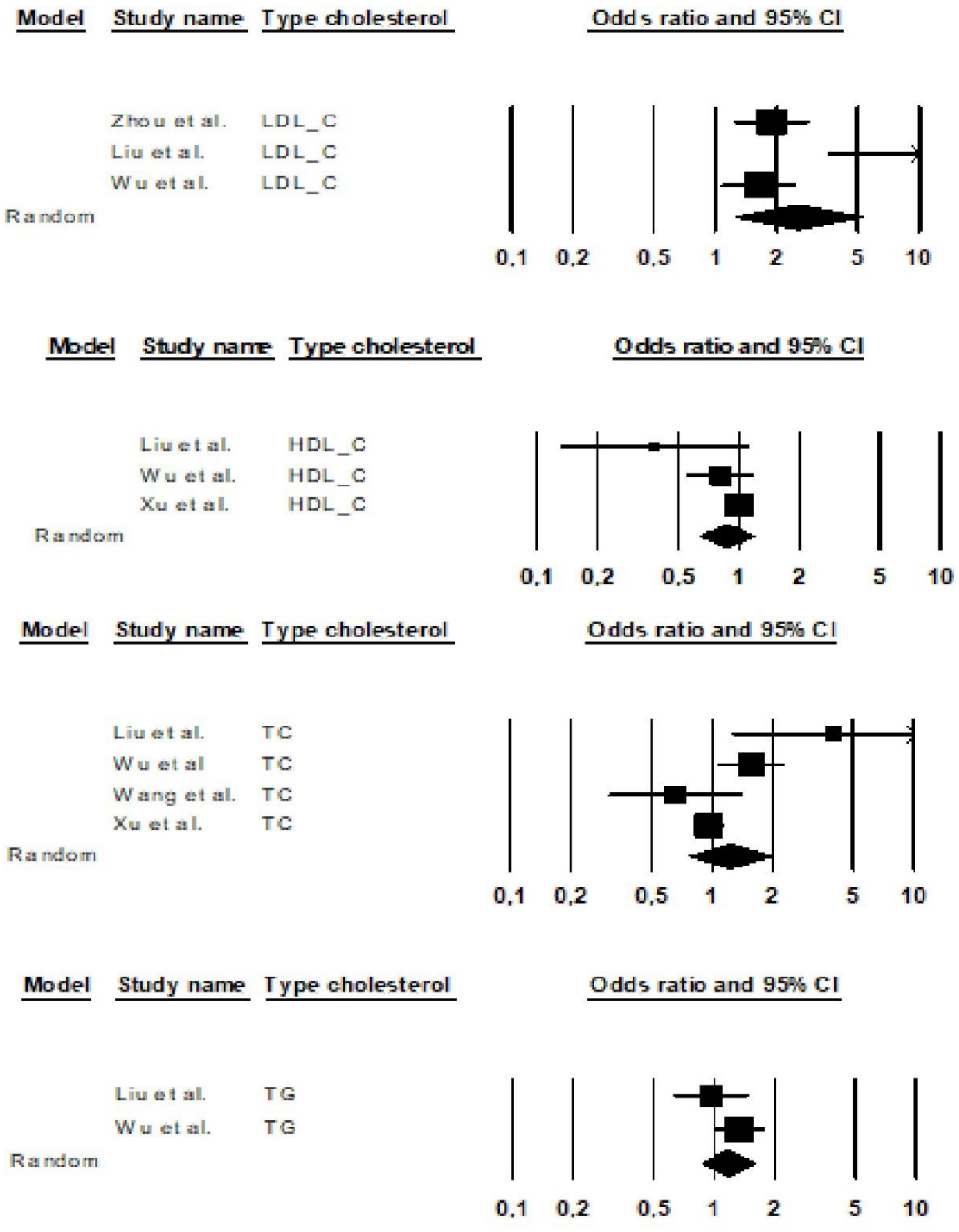

Figura 3. Forest plot of the effects of dyslipidemia on Alzheimer's disease (AD): low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG).

3.1. Studies of LDL-C Levels

The total random effect of LDL-C levels on AD was significant for k = 3 meta-analysis (N = 17,764, n = 5693 AD, and n = 12,071 HCs): OR = 2.55, 95% CI [1.25, 5.22], Z = 2.57, p = 0.010, d = 0.52.

The first study conducted by Zhou et al. (31) provided information of K = 20 studies that compared serum LDL-C levels in AD and HC subjects (N = 7033 participants: 2266 AD and 4767 HCs). Liu et al. (8) also compared AD (n = 584 AD) and HC participants (n = 2130), examining K= 9 independent studies with an N = 2714. Finally, Wu et al. (32) informed about LDL-C, comparing K= 33 studies (N = 8017) with n = 2843 AD and n = 5174 HC participants. Results indicated that the LDL-C serum levels were significantly higher in AD patients than in HC subjects. Heterogeneity was significant (Q = 9.05, df = 2; I^2 = 77.89%, p = 0.011, I^2 = 77.89%). (See Table 3).

Tabla 3. Summary effect sizes for low-density lipid cholesterol (LDL-C) serum levels and Alzheimer's disease (AD).

Model	**Study**	**Statistics**						
		OR	***LL***	***UL***	***Z***	***p***	**Weight Random**	***Std* Residual**
	Zhou et al. (31)	1.89	1.24	2.86	2.98	0.003	40.64	−0.69
	Liu et al. (8)	12.67	3.56	45.08	3.92	0.000	18.96	2.13
	Wu et al. (32)	1.64	1.07	2.50	2.25	0.024	40.39	−1.01
Random effect		2.55	1.25	5.22	2.57	0.010		

OR: Odds Ratio; LL: Lower Limit; UL: Upper Llimit; Z: standard punctuation; p: statistical significance; Std: Standard Residual.

3.2. Studies on HDL-C Levels

Three meta-analyses K = 3 (N = 23,642, n = 4147 AD and n = 19,495 HCs) showed a non-significant effect of HDL-C levels on the risk of AD: OR = 0.87, CI 95% [0.64, 1.18], Z = −0.89, p = 0.372, d = 0.08.

Liu et al. (8) included 11 studies that analyzed HDL-C serum levels in AD patients and HCs. The combined sample size consisted of 2960 participants: 727 AD and 2233 HCs. They found non-significant differences between AD and HC subjects in HDL-C serum levels. Likewise, no differences were found between AD and HCs (K = 33 studies; N = 8192, n = 2921 AD and n = 5271 HCs) in the meta-analysis conducted by Wu et al. (32). Finally, Xu et al.(43) did not find any association between a lower level of HDL-C and AD (K = 6 studies; N = 12,490, n = 499 AD and n = 11,991 HCs). Heterogeneity was non-significant (Q = 3.85, df = 2; I^2 = 47.98%, p = 0.146). (See Table 4).

Tabla 4. Summary effect sizes for high-density lipid cholesterol (HDL-C) serum levels and AD.

Model	**Study**	**Statistics**						
		OR	***LL***	***UL***	***Z***	***p***	**Weight Random**	***Std* Residual**
	Liu et al. (8)	0.38	0.13	1.13	−1.7	0.081	7.35	−1.46
	Wu et al. (32)	12.67	3.56	45.08	3.92	0.000	18.96	2.13
	Xu et al. (43)	1.00	0.87	1.16	0.00	1.000	59.35	1.08
Random		0.87	0.87	0.87	0.87	0.87		

OR: Odds Ratio; LL: Lower Limit; UL: Upper Llimit; Z: standard punctuation; p: statistical significance; Std: Standard Residual.

3.3. Studies on TC Levels

Results indicated that K = 4 meta-analyses (N = 2,271,785, n = 16,704 AD and n = 2,255,081 HCs) informed about the TC and AD risk. The combined effect size showed that TC levels increased by 44% the risk of AD, but this effect did not reach statistical significance: OR = 1.44, CI 95% [0.91, 2.28], Z = 1.55, p = 0.121, d = 0.20.

Liu et al. (8) included k = 13 primary studies (N = 3112) that compared the TC serum levels in AD (n = 809) and HC subjects (n = 2303), showing that TC levels were significantly higher in AD patients than in HC participants. Likewise, Wu et al. (32) reviewed K = 33 studies (N = 7850, n = 2661 AD patients and n = 5189 HCs), finding significant effects. However, Wang et al. (57) evaluated total of K= 16 studies (N = 1653), including 959 subjects with AD

and 694 controls, finding non-significant differences between AD and HDs. In this study, the authors analyzed the markers of cholesterol in subjects with AD with age-matched controls. Finally, Xu et al. (43), in a longitudinal study, also reported non-significant differences between AD and HCs in TC levels (K = 16 studies; N = 2,259,170, n = 12,275 AD and n = 2,246,895 HCs). Heterogeneity was significant (Q = 11.83, df = 3; I^2 = 74.77%, p = 0.008). (See Table 5).

Tabla 5. Summary effect sizes for total cholesterol (TC) serum levels and Alzheimer's disease (AD).

Model	Study	Statistics						
		OR	***LL***	***UL***	***Z***	***p***	**Weight Random**	***Std* Residual**
	Liu et al. (8)	3.97	1.25	12.55	2.35	0.019	11.41	1.55
	Wu et al. (32)	1.57	1.09	2.28	2.39	0.017	31.52	0.26
	Wang et al. (57)	1.52	0.70	3.25	1.07	0.283	19.04	0.11
	Xu et al. (43)	0.96	0.83	1.12	-0.53	0.597	37.25	0.38
Random effect		1.44	0.91	2.28	1.55	0.121		

OR: Odds Ratio; LL: Lower Limit; UL: Upper Llimit; Z: standard punctuation; p: statistical significance; Std: Standard Residual.

3.4. Studies of TG Levels

The combined effect size of studies of TG levels K = 2 (N = 8085, n = 2865 AD and n = 5220 HCs), OR = 1.22, CI 95% [0.96, 1.56], Z = 1.64, p = 0.102, d = 0.11, indicates that there was no significant association between overall TG and the risk of AD. Liu et al. (8) (K = 6; N = 512, n = 273 AD, and n = 239 HCs) and Wu et al. (32) (K = 28; N = 7573, n = 2592 AD and n = 4981 HCs) showed that there were no differences in TG serum levels between patients and controls. Heterogeneity analysis was non-significant (Q = 0.91, df = 1; I^2 = 0%, p = 0.340). (See Table 6).

Tabla 6. Summary effect sizes for triglycerides (TG) serum levels and Alzheimer's disease (AD).

Model	Study	Statistics						
		OR	***LL***	***UL***	***Z***	***p***	**Weight Random**	***Std* Residual**
	Liu et al. [1]	1.04	0.68	1.57	0.17	0.864	33.61	−0.96
	Wu et al. [12]	1.33	0.99	1.79	1.89	0.059	66.39	0.96
Random effect		1.22	0.96	1.56	1.64	0.102		

OR: Odds Ratio; LL: Lower Limit; UL: Upper Llimit; Z: standard punctuation; p: statistical significance; Std: Standard Residual.

DISCUSSION

This study analyzes the association between cholesterol levels and the risk of developing AD. This is the first attempt to evaluate this relation by identifying previous meta-analyses and their primary studies analyzed worldwide. The present meta-meta-analysis summarizes the information of 100 primary studies and expands the findings of individual studies.

Global results revealed that the level of cholesterol is a risk factor for AD. This finding is consistent with those from several prior studies, in which high cholesterol levels were associated with a higher likelihood of developing AD (8,32,43,83). However, sensitivity analysis yielded several interesting and informative results. Even though the studies revealed that AD is involved in lipid metabolism, the results indicated that the effect of LDL-C, HDL-C, TC and TG on the development of dementia was different. We found that, compared with HC subjects, LDL-C levels were higher in AD participants, whereas HDL-C, TC and TG levels were not sensitive hallmarks of AD.

An elevated LDL cholesterol level was an independent risk factor for the development of AD. The pooled effect size exhibited a significant increase in the risk of AD for individuals with higher levels of LDL-C. Other prospective studies also support these results, showing that LDL concentration in mid-life increases the risk of developing AD in later life (105). Nevertheless, in this study, the pathways through which elevated LDL cholesterol levels influence the development of dementia are unclear (63).

First, previous research indicated that the senile plaques theories may provide a link between high LDL-C and AD (62). In this theory, elevated levels of LDL-C and TC cause the extracellular deposition of amyloid protein (Aβ), hindering neuronal synaptic connections in the brain and increasing the risk of AD (106).

Second, the Tau protein may play an important role in proper axonal transport and overall neural integrity (107) and correlates with cognitive decline in the AD. In this case, cognitive loss is associated with an excess of the Tau protein, which causes neurofibrillary tangles and prevents the synaptic connection of neurons in the brain (108).

In addition, risk factors for vascular disease may also be risk factors for AD, and high blood LDL-C levels are vascular risk factors (109). Indeed, various studies have demonstrated that high concentrations of LDL cholesterol are associated with coronary heart disease and carotid artery atherosclerosis, which, in turn, may lead to cognitive decline through cerebral embolism or hypoperfusion (110–113). The study conducted by Moroney et al. (113) also demonstrated that the level of LDL cholesterol is a potential risk factor for dementia with stroke. Therefore, it is necessary to analyze the influence of other factors related to LDL-C in the development of AD. This result could explain the heterogeneity between LDL-C studies found in this meta-meta-analysis.

The results showed no difference in HDL-C serum levels between AD and HC subjects. However, this result remains controversial, and no conclusive evidence was found. Various studies indicated that variations in HDL serum lipid levels are not associated with AD (8,32,43,63). In other studies, lower levels of HDL have been associated with a high risk of AD (106,109). Conversely, evidence suggests that high HDL-C levels are associated with a reduced risk of dementia, and that HDL may protect people against cerebrovascular dysfunction in AD (114). In fact, cholesterol is an essential molecule for many physiologic processes and has multiple beneficial effects. Cholesterol is a precursor of steroid hormones

(estrogens, androgens, vitamin D), it provides structural integrity and modulates the fluidity of cell membranes and is a main component of basic synaptic integrity and neurotransmission (115). Moreover, HDL is known to have antioxidant and anti-inflammatory properties, which can affect neuroinflammatory responses in the brain and improve cognitive functions (116).

Whereas TC (total cholesterol) has been identified as a lipid marker for hyperlipemia (8,32,57), the summarized results did not find significant effects of TC levels on AD. Four meta-analyses assessing the effects of mid-life serum cholesterol on late-life risk of dementia and AD have yielded conflicting results. Several studies state that high cholesterol levels in middle age represent a risk factor for AD, but that there are no detectable differences in cholesterol levels at advanced ages (31,63,114). Therefore, the non-significant effects of TC on AD in prospective studies (30 years to follow-up) could be explained by the variations in TC levels and the disease progression. Along these lines, Lepara et al. (115) indicated that cholesterol may be associated with AD cross-sectionally. In the same vein, Reitz et al. (106) concluded that there is an association between higher cholesterol levels and a lower risk of AD, because of the nutritional status of elderly patients. In the early stages of AD, patients show alterations in the energy profile (weight loss, reduced caloric intake and increased energy requirements), and low cholesterol levels may reflect malnutrition (115). Similarly, experimental studies and retrospective analyses in cohort studies indicate that statins could also affect the natural progress of the AD and reduce its prevalence over time (116). Finally, even though Wang et al. (57) used a cross-sectional design, they did not find significant effects of TC on AD. In this study, the authors explained that cholesterol homeostasis could be altered in preclinical AD, whereas cholesterol dysregulation occurs throughout the disease's process. This evidence could make it more difficult to find a significant relationship between TC and AD during the disease's progress (57). Hence, additional analysis is necessary.

The triglyceride serum level did not show a positive association with the development of AD in this meta-meta-analysis. This result also may be explained because of the retrospective design of some of the studies included herein. As we noted before, the use of cholesterol-lowering drugs could have suppressed the development of AD in participants, decreasing the likelihood of finding an association between TC and AD (117,118). For instance, Wolozin et al. (117) concluded that the use of statins, including lovastatin and pravastatin, decreased the development of AD. Other studies did not find that high triglyceride levels were associated with AD (8,32) and with potential changes in cognitive performance (119). However, the results are not robust. Many studies associate hypercholesterolemia with the risk of dementia. Kivipelto et al. (120) concluded that hypercholesterolemia could increase the risk of dementia, because arteriosclerosis occurs in the blood vessels, and this can alter blood flow, and directly induce neurodegeneration of AD (121). Likewise, a recent study that investigated the association between diet and the level of triglycerides in the blood concluded that TG was associated with cognitive decline (122). This result highlighted that a healthy diet and a good lifestyle for controlling the serum lipid levels was beneficial for preventing AD, which seems to counteract the scientific literature, where TG level is not associated with AD (123).

Our summary results showed no statistically significant differences between serum HDL-C, TC and TG levels in patients with AD compared with HC participants. Based on all available information, this study reveals that it is important to identify early risk factors for AD, because the neurodegenerative processes of AD can begin at an early age, and pharmacological and non-pharmacological therapies that delay the neurodegenerative progress of AD may be performed. Moreover, it may be necessary for future studies to investigate in more detail the neural regions that exhibit different cholesterol content regarding the pathological processes related to AD (124), and the influence of other potential moderators that could explain the heterogeneity between the primary results. Hence, the

relevance of our findings for the pathophysiology of AD needs to be further explored in future research.

The limitations of this study include the possibility of misclassification bias when using single baseline measurements of cholesterol and the lack of verification of the clinical diagnosis of dementia subtype. We were also unable to investigate the effect of other moderator variables, such as country or cohort. Perhaps the relationship between lipid levels and the risk of probable AD would change if the same cohort were analyzed. Moreover, we could not assess the possible association between dietary and exercise levels and LDL-C, HDL-C, TC and TG serum levels. In addition, other variables have been associated with AD, but the meta-analysis included lacked a description of these factors, so the results could not be further adjusted. Body mass index, smoking status, stroke, hypertension, Type 2 diabetes and heart disease are also closely related to blood lipid levels, and could affect the risk of AD.

However, this meta-meta-analysis represents a step toward evidence-based of AD and its relationship with dyslipidemia. First, this meta-meta-analysis provides an update and complete summary of the association of LDL-C, HDL-C, TC and TG with the prevalence of AD. Second, the effect sizes of one of the most studied risk factors for AD are provided to all healthcare professionals. Cholesterol is a modifiable risk factor, so if professionals know the relationship between cholesterol and AD, they could try to modify cholesterol levels to help to reduce AD risk. This study provides empirical evidence for the reduction of LDL-C levels through the promotion of healthy lifestyles (such as diet, weight control or physical activity) and/or the prescription of different medical treatments.

CONCLUSIONS

To sum up, the association of cholesterol and AD was evaluated. This meta-meta-analysis indicates that there is an association between the effect of cholesterol and AD. LDL-C, HDL-C, TC and TG were analyzed separately. LDL-C has a significant impact on the

development of AD. Overall, this meta-meta-analysis represents a step toward evidence-based knowledge of AD.

The understanding of risk factors and protective factors of AD would require more long-term studies, conducting exhaustive follow-ups of each patient. Furthermore, this study highlighted the need to analyze other factors related to AD. Indeed, physical activity and the use of drugs could reduce the effects of cholesterol on AD; hence, more research is necessary. This meta-meta-analysis provides more knowledge about the relationship between cholesterol and AD, which could have a huge beneficial impact on AD incidence and prevalence.

CAPÍTULO 3

"Pide una mano que estreche la suya, un corazón que le cuide y una mente que piense por él cuando él no pueda hacerlo; alguien que le proteja en su viaje a través de los peligrosos recodos y curvas del laberinto".

(Vivir en el Laberinto. Diana Friel, 1994)

Sáiz-Vázquez O, Gracia-García P, Ubillos-Landa S, Puente-Martínez A, Casado-Yusta S, Olaya B et al. Depression as a risk factor for Alzheimer's disease: a systematic review of longitudinal meta-analyses. J Clin Med. 2021; 10(9), 1809. https://doi.org/10.3390/jcm10091809

CAPÍTULO 3: DEPRESSION AS A RISK FACTOR FOR ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW OF LONGITUDINAL META-ANALYSES

ABSTRACT

Background: Alzheimer's disease (AD) is the most frequent cause of dementia, linked to morbidity and mortality among elderly patients. Recently, several clinical studies suggested that depression is a potential risk factor for cognitive decline and AD.

Methods: A review of meta-analyses was performed, calculating pooled odds ratios to estimate the risk of AD in people with a prior diagnosis (or clinically significant symptoms) of depression.

Results: A total of six meta-analyses which represented 28 individual studies were analyzed. A significant association between depression and AD was found (*OR* = 1.54, 95% *CI* [1.02–2.31]; $p = 0.038$). The results showed that heterogeneity across studies was substantial. We found a significant positive effect size for clinical measures of depression, but not for symptomatic rating scales, in the association of depression with risk of AD. The type of rating scale used to assess depression and the cut-off criteria selected also moderated the relationship between depression and AD risk.

Conclusions: We found that studies that used clinically significant criteria for diagnosis of depression had more consistent and significant results than studies that used symptomatic scales.

Keywords: depression; Alzheimer's disease; clinical and symptomatic criteria; meta-meta-analysis

INTRODUCTION

Alzheimer's disease (AD) is the most frequent cause of dementia and is considered one of the main causes of morbidity and mortality among elderly people (125). The World Alzheimer's Report revealed that 46.8 million people worldwide were living with dementia in 2015, and the total global social cost of dementia was estimated to be $818 billion (126). Estimates of dementia incidence in population-based studies range from 5 to 10 cases per 1,000 person-years in people aged 64 to 69, and up to 40 to 60 cases per 1,000 person-years in people aged 80 to 84 (127).In 2017 in Europe, prevalence rates of AD have been reported to be 5.05%, 3.31% in men, and 7.13% in women (128). Given the personal and social consequences of dementia and AD demand, we accelerate the global effort to understand this complex disorder (129).

Decades of research has suggested that the pathophysiological mechanisms underlining this neurodegenerative disease includes the accumulation of the amyloid-beta peptide (Aβ) in brain tissues and to cytoskeletal changes related to the hyperphosphorylation of microtubule-associated Tau protein in neurons. As a consequence, neuritic plaques and neurofibrillary tangles are accumulated, mostly observed in medial temporal lobe and associative neocortical areas (130) and resulting in several cognitive deficits. The clinical manifestation of AD is progressive, from unnoticeable brain changes to brain changes that cause cognitive deterioration and eventually physical disability (131). AD usually begins with memory difficulties followed by other cognitive problems such as visuospatial abnormalities, navigation difficulties, executive problems, and language disturbance (126).

Evidence seems to suggest that the etiology of AD is multifactorial, with genetics, older age, and a family history of AD being the greatest contributors to a higher risk of AD (132). Furthermore, AD is often associated with other chronic diseases (diabetes, cholesterol, cardiovascular diseases, obesity, and hypertension) (133). Although these risk factors are

unchangeable, other risk factors can be modified to reduce the risk of dementia and cognitive decline. This is particularly important, since there is no currently available way to stop the damage and destruction of neurons linked to AD.

Depressive symptoms are common in AD and occur in approximately 20–30% of patients (134). Depression is a serious medical illness that affects about 300 million people worldwide and which might aggravate existing medical conditions and increase functional disability (134,135). Clinical evidence suggests a relationship between depression and AD (136–139). However, it remains unclear whether depression represents a risk factor for AD, is an early symptom of neurodegeneration, or is a reaction to early cognitive deficits (139,140). Some studies have suggested that depressive symptoms immediately follow the onset of AD rather than precede it (141). Moreover, evidence from other studies indicates that depression has only a mild effect on dementia (142) and does not increase the risk for developing AD (143). However, other authors suggest that the presence of depression in patients with AD increases the risk of behavioral disturbance and accelerates functional decline (137). Hudon et al. (144), for example, found that depression was the most consistent risk factor associated with behavioral or psychological symptoms and cognitive decline in patients with AD. In addition, several studies concluded that late-life depression is related to an increased risk for all-cause dementia, vascular dementia, and Alzheimer's disease (33,34,36), and late-life depression was shown to be associated consistently with a two-fold increased risk of dementia (35,37).

In order to clarify the role of depression as a risk factor of AD, several meta-analyses were conducted (34,36,37,144). However, some limitations were pointed out. Cherbuin et al. (35), for example, indicated that, in general, results from previous studies that focused on depression as a risk factor of AD might be biased due to the type of instrument used to assess depression. Results are frequently based on different tools. Some of these studies are

based on symptomatic rating scales with cut-off points (e.g., CESD), while others are based on clinical criteria (e.g., DSM). Thus, the pooled estimates of the risk for AD in depressed people might be unreliable, because these meta-analyses combined effect sizes from studies using different instruments to assess depression (i.e., symptomatic rating scales and clinical diagnoses). Additionally, these previous meta-analyses did not pool findings separately for studies using clinical criteria and studies using depressive symptom rating scales with specified cut-off points.

Based on these limitations and the inconclusive evidence, we aimed to perform a meta-meta-analysis of longitudinal studies to assess the effect of depression on the risk of a subsequent diagnosis of AD. Given the expected heterogeneity among studies, we also aimed to pool findings separately from studies using clinical criteria and those using de-pression symptom rating scales, and to test the association between depression and risk of AD according to the different instruments used.

MATERIALS AND METHODS

I. Data Collection

This meta-meta-analysis was performed in accordance with the Preferred Reporting for Systematic Reviews and Meta-analysis (PRISMA) Statement (145). For data collection, we searched meta-analyses that measured depression at baseline and reported outcomes in individuals with diagnoses of AD at follow-up. ISI Web of Science (WOS), Scopus, Pubmed, Elsevier Science Direct, and Google scholar were searched from inception up to 31 July 2020. Combinations of the following search terms were used: "depression" AND "Alzheimer's disease" AND "meta-analysis". The data search was done in English (four studies) and Spanish (one study). When necessary, corresponding authors were contacted to provide full text details of the study outcome measures.

II. Inclusion Criteria

By consensus of the authors, studies were included if they met the following criteria:

- Longitudinal studies that investigated the effect of depression or depressive symptoms (at baseline) as an antecedent to AD (follow-up).
- Studies including patients with a diagnosis of AD according to diagnosis criteria (e.g., Related Disorders Association criteria, N-ADRDA, the Diagnostic and Statistical Manual of mental Disorders, DSM-III or the National Institute of Neurological and Communication Disorders-Alzheimer's Disease).
- Studies that clinically assessed levels of depression by means of a clinical diagnosis (e.g., DSM-IV, ICD-10), or a symptomatic diagnostic tool with a cut-off score (e.g., Geriatric Mental State Schedule, GMS) that identifies clinically significant levels of depression.
- Studies reporting sufficient information to calculate common effect size statistics (i.e., mean and SD, exact P-, t-, or z-values).
- Original, peer-reviewed meta-analyses that were published in English and Spanish.

III. Exclusion Criteria

By consensus of the authors, the following were excluded:

- Studies investigating the association of depression and risk of AD using a sample of patients with AD and other dementia (non-independent or overlapping data for AD).
- Studies not reporting quantitative data to calculate the association between depression and AD, or not published as meta-analyses in peer-reviewed journals (i.e., conference abstracts, book chapters).
- Meta-analyses about other topics or those that included the same primary studies.

IV. Data Extraction and Quality Assessment

Titles and abstracts of potential meta-analyses about depression and incident AD were independently analyzed by three researchers (OS, SU, PG). After exclusion of irrelevant articles, the remaining meta-analyses were critically inspected to check data accuracy. Then, full texts of all primary studies included in each meta-analysis were screened according to the inclusion criteria. In the event of ambiguity, two authors (SU, JS) additionally reviewed the study to reach a consensus regarding its eligibility.

Data related to the diagnosis/assessment of depression and AD were collected directly from the text or from statistical tables. The lead author and either the third or fourth author independently extracted data from each study, including study characteristics (year, country, total sample size, and length of follow-up period), sample characteristics (mean age, % of women), measures of depression and AD, and the cut-off point used for depression in each individual study.

Diagnoses of AD were based on the following accepted clinical criteria: Revised criteria and the National Institute of Neurological and Communication Disorders-Alzheimer's Disease and Related Disorders Association criteria (N-ADRDA), the Diagnostic and Statistical Manual of Mental Disorders in different editions (DSM-III, DSM-III-R, DSM-IV, DSM-V), and the International Classification of diseases (ICD-10). Additionally, studies established different cut-off scores on neuropsychological tests for the purposes of screening out cognitive impairment and dementia at baseline (see Table 7). Participants with scores above the cut-off on cognitive domains were excluded on the basis that this level of test performance indicates the presence of dementia or cognitive impairment. The most frequently used measures to describe the cognitive characterization of the participants at baseline were the Mini Mental State Examination (MMSE) (n = 14) and the Clinical Rating Scale (CRS) (n = 6). Diagnoses of depression were based on either symptomatic rating scales

or clinical diagnoses. Clinical criteria for depression included the DSM-III, DSM-III-R, DSM-IV, DSM-V, and the Automated Geriatric Examination for Computer Assisted Taxonomy (GMS-AGECAT). Diagnoses of depression were based on symptomatic rating scales on valid cut-off points (SGDS/15/30, CES-D/10/11/20, HRSD-17).

In addition, the quality of the included studies was reported using the Assessment of Multiple Systematic Reviews (AMSTAR) tool (28), which was previously shown to have good interrater agreement, reliability, and content validity (28,29).

V. Statistical Analysis

Crude odds ratios (*ORs*) (and 95% confidence intervals (*CIs*)) were used to calculate the risk of developing AD associated with previous depression. When the number of cases of depression and AD were not provided, the effect sizes were calculated using reported data in the meta-analysis according to Lipsey and Wilson (146). We considered *HRs* and *ORs* as equivalent, since it was previously shown that for rare events, they can be considered equivalent (incidence < 15%) (100). Seventeen studies provided data that could be used in calculating crude *ORs* (odds of an outcome in the intervention arm divided by the odds of an outcome in the control). Eleven additional studies provided data on AD risk in samples as *HR* or *ORs* with 95% confidence intervals that could be used in pooling estimates.

Tabla 7. Summary of demographic and study information

Study	Year	Country	AD Measure [1]	Cognitive Measure [2]	Cut-Off Criteria Cognition	Depression Measure [3]	Cut-Off Criteria Depression [4]	*n*[5]	Follow-Up Length (Years) *M* (*SD*)	Age *M* (*SD*)	Female (*%*) (Total)	AMSTAR2 [6]
Bae et al. (147)	2015	AS	N-ADRDA	CERAD-K	≥60	GDS15	≥8	540	3.5 (0.3)	71.7 (5.1)	55.2	HIGH
Bartolini et al. (148)	2005	EU	N-ADRDA	MMSE	>26	DSM-III-R	-	222	1	69.2 (4.8)	63.5	HIGH
Becker et al. (143)	2009	USA	N-ADRDA	MMSE	>26	CES-D20	≥10	729	7.1 (NR)	70	69	HIGH
Blasko et al. (149)	2010	Austria	N-ADRDA	CERAD	≥60	DSM-IV	-	648	2.5 (NR)	78.3 (0.5)	56.5	HIGH
Burke et al. (150)	2018	USA	N-ADRDA	CRS	≤3	DSM-V	-	12,083	4.2 (-)	63.9	83	HIGH
Chen et al. (151)	1999	USA	DSM-III-R	MMSE	>26	CES-D20	≥16	803	4.5 (NR)	73.7 (5.0)	60	MODERATE
Dal Forno et al. (152)	2005	USA	N-ADRDA	BIMC		CES-D20	≥20	1357	6.1 (-)	65.5 (12.0)	45.5	HIGH
Devanand et al.(153)	1996	USA	N-ADRDA	CRS	≤3	DSM-III R	-	456	2.54	72	70	HIGH
Dotson, Beydoun & Zonderman (154)	2010	USA	DSM-III R	BIMC		CES-D20	≥16	2177	23.6 (NR)	52.7 (18.8)	42.3	HIGH
Fuhrer, Dufouil & Dartigues (155)	2003	France	N-ADRDA/DSM-III-R	MMSE	>26	CES-D20	≥16	1576	8.0 (NR)	75.2 (6.9)	58.3	HIGH
Gatz et al. (141)	2005	Canada	DSM-III R	MMSE	>26	CES-D20	≥16	766	5	74.5 (6.0)	61.7	HIGH
Geerlings et al. (156)	2000	Países Bajos	DSM-III-R	MMSE	>26	GMS-AGECAT	-	1911	5,9 (1,6)	73.5 (7.9)	49	MODERATE

Study	Year	Country	AD Measure [1]	Cognitive Measure [2]	Cut-Off Criteria Cognition	Depression Measure [3]	Cut-Off Criteria Depression [4]	*n*[5]	Follow-Up Length (Years) *M* (*SD*)	Age *M* (*SD*)	Female (*%*) (Total)	AMSTAR2 [6]
Geerlings et al. (157)	2008	Netherlands	N-ADRDA	MMSE	>26	CES-D20	≥16	393	5.9 (1.6)	73.5 (7.9)	49	MODERATE
Gracia-García et al. (158)	2015	EU	DSM-IV	MMSE	>26	GMS-AGECAT	≥3	3626	4.5	71.9 (9.0)	54.4	HIGH
Heser et al. (159)	2013	Germany	DSM-IV/ICD-10	MMSE	>26	DSM-IV	-	2969	4	81	64.8	HIGH
Irie et al. (160)	2008	USA	N-ADRDA	CRS	≤3	CES-D11	≥9	1585	5.1	76.3 (3.6)	0	HIGH
Kim et al. (161)	2010	South Korea	N-ADRDA	CRS	≤3	GDS30	13/14	473	2.4 (0.3)	71.8 (5.1)	54.4	HIGH
Kim et al. (162)	2011	South Korea	DSM-IV	CRS	≤3	GMS-AGECAT	≥3	563	2.4 (0.3)	71.8 (5.0)	54.4	MODERATE
Lauriola et al. (163)	2018	EU	DSM-V	MMSE	>26	DSM-V	-	181	4	74.5 (7.5)	59.7	HIGH
Lenoir et al. (164)	2011	France	N-ADRDA	MMSE	>26	CES-D20	M ≥ 16 W ≥ 22	7989	4 (NR)	74.0 (5.4)	61.3	HIGH
Li et al. (165)	2011	USA	N-ADRDA	CASI	≥78	CES-D11	≥10/	3410	7.1 (NR)	74.9 (6.2)	59.9	HIGH
Luchsinger et al. (166)	2008	USA	N-ADRDA	CRS	≤3	HRSD17	≥10	1138	5.1 (3.3)	75.1 (6.4)	67.7	HIGH
Reding, Haycox & Blass (167)	1985	USA	ICD-10	MSQ	0–2 errors	DSM-III	-	60	3	-	-	MODERATE
Richard et al. (168)	2013	USA	DSM-III R	MMSE	>26	CES-D10	≥4	2160	-	76.9 (7.1)	75	MODERATE

Study	Year	Country	AD Measure [1]	Cognitive Measure [2]	Cut-Off Criteria Cognition	Depression Measure [3]	Cut-Off Criteria Depression [4]	*n*[5]	Follow-Up Length (Years) *M* (*SD*)	Age *M* (*SD*)	Female (%) (Total)	AMSTAR2 [6]
Saczynski et al. (169)	2010	USA	N-ADRDA	MMSE	>26	CES-D20	≥16	949	8 (NR)	79.3 (5.0)	63.6	MODERATE
Tyas et al. (170)	2001	Canada	N-ADRDA	MMSE	>26	CES-D20	≥16	694	3 to 5	65	67	MODERATE
Vilalta-Franch et al. (171)	2013	EU	DSM-IV	CAMCOG	≥79	DSM-IV	-	451	5	76.7 (5.4)	63.7	HIGH
Wilson et al. (172)	2003	USA	N-ADRDA	VARIOUS	-	CES-D10	≥4	142	3.9 (NR)	81.0 (6.6)	52.3	HIGH

Note: Meta-analyses analyzed were: Cherbuin et al. (35), Diniz et al. (36), Gao et al. (37), Kuring et al. (34), Kuring et al. (173), Santabárbara et al. (33). [1] AD: Alzheimer's disease. DSM-III-R, DSM-IV, DSM-V = Diagnostic and Statistical Manual of Mental Disorders; N-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; N-AIREN = National Institute of Neurological and Communicative Disorders and Stroke–Association Internationale pour la Recherche et l' Enseignement en Neurosciences; ICD-10 = International Classification of Diseases. Total of diagnoses are *k* = 30. [2] Cognitive measures: CERAD/K: Consortium to Establish a Registry for Alzheimer's Disease; MMSE: Mini-Mental State Examination; CRS: Clinical Rating Scale; BIMC: Blessed Information-Memory-Concentration; CASI: Cognitive Abilities Screening Instrument; MSQ: Mental Status Questionnaire; CAMCOG: Cambridge Cognitive Examination. [3] Depression. DSM-III, DSM-III-R, DSM-IV, DSM-V: Diagnostic and Statistical Manual of Mental Disorders; HRSD17: Hamilton M. Rating Scale for DP; GMS-AGECAT: Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy; GDS-15/30: Geriatric Depression Scale; CES/-D10 (10 items)/- D11 (11 items)/-D20 (20 items) = Center for Epidemiologic Studies–DP Scale. [4] Cut-off criteria for categorial depression measures: HRSD-17, Hamilton et al.(174); Williams et al. (175); GMS-AGECAT, Copeland et al. (176); GDS 15/30, Jung et al. (177); Yesavage et al. (178); SGDS, Kim et al. (179); CES-D/D20, Radloff (180); CES-D10/11, Kohout et al. (181). [5] Follow-up: Total sample size for controls and healthy indicated; separate sample sizes for those with AD and depression and healthy controls were not reported. Study based on registry data. [6] AMSTAR 2 identifies quality of randomized controlled clinical trials. Rating overall confidence in the results: High = Zero or one non-critical weakness; Moderate = More than one non-critical weakness; Low = One critical flaw with or without non-critical weaknesses; Critically low = More than one critical flaw with or without non-critical weaknesses, Shea et al. (28) (https://amstar.ca/Amstar_Checklist.php accessed on 19 April 2021)

Summary statistics were calculated using Comprehensive Meta-Analysis software (CMA; Version 3) (Biostat Inc., Englewood, NJ, USA) (102,103). Initially, we performed an analysis summarizing all data available, including all studies with validated cut-offs or clinical diagnoses in a single pooled estimate (102). For each study, we calculated: (a) 95% *CI* of the effect, (b) *Z* value and *p* (two-tailed significance), and (c) *k* or number of studies(182). Presence of publication bias was assessed through visual inspection of funnel plots and with Egger's test (182).

The level of heterogeneity was assessed with the I^2 statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance alone. An I^2 value of 25% indicates low heterogeneity, 50% moderate heterogeneity, and 75% high heterogeneity (102). Random-effect models were used to determine statistically significant heterogeneity. Additionally, the Cochran *Q* test was applied to assess significant heterogeneity (*p*-value < 0.05). Moderating variables were selected on the basis of substantive considerations and the availability of data across studies included in the meta-analysis. Subgroup analyses were performed according to how depression was assessed: by clinical diagnosis (e.g., DSM-V) or by symptomatic rating scales (e.g., CES-D). Additionally, because the studies included different symptomatic rating scales, we also considered the instrument and the specific cut-off criteria as moderating variables. Therefore, we calculated the effect sizes of the association between depression and risk of AD separately for studies using different cut-off points. Finally, meta-regression analyses were conducted to obtain the proportion of variance explained for each moderator (the *R*-square analog). The scatter plot represents the mean effect for each level of covariate.

RESULTS

The search strategy produced a total of 443 meta-analyses (see Table 7). Initially, 37 meta-analyses were eligible for inclusion. Of these, 31 were excluded: (a) 3 did not report an effect size; (b) 6 did not provide information on the relationship between depression and AD; (c) 8 were duplicates; (d) 9 were systematic reviews about other topics; (e) 4 aimed to study the effect of medication on AD; and (f) 1 included the same primary studies as another. Finally, a total of six meta-analyses were analyzed (k = 28 pooled effect sizes), representing data from n = 28 individual studies (see Figure 4).

Since the effect estimated from a biased collection of studies might overestimate the true effect, we assessed the likely extent of this bias and its potential impact on the conclusions. The result of Egger's test was not significant: The intercept (B0) was 0.53, 95% *CI* (−1.88 to 2.95), with t = 0.45, df = 26, p = 0.65, indicating no publication bias.

I. Overall Results from the Meta-Analysis

A total of 28 individual studies reported the association between depression at baseline and AD at follow-up with a total of 101,881 participants (*N*baseline = 51,830; *N*follow-up = 50,051). Individual sample sizes ranged from 60 to 12,083. Most subjects was female. The mean age was 71.95, ranging from 52.7 to 81 years. One study did not report gender and age (167). The mean follow-up length was 4.90 years (range from 1 to 23.6), with one study not reporting the number of years (168). Characteristics of the 28 individual studies are presented in Table 8.

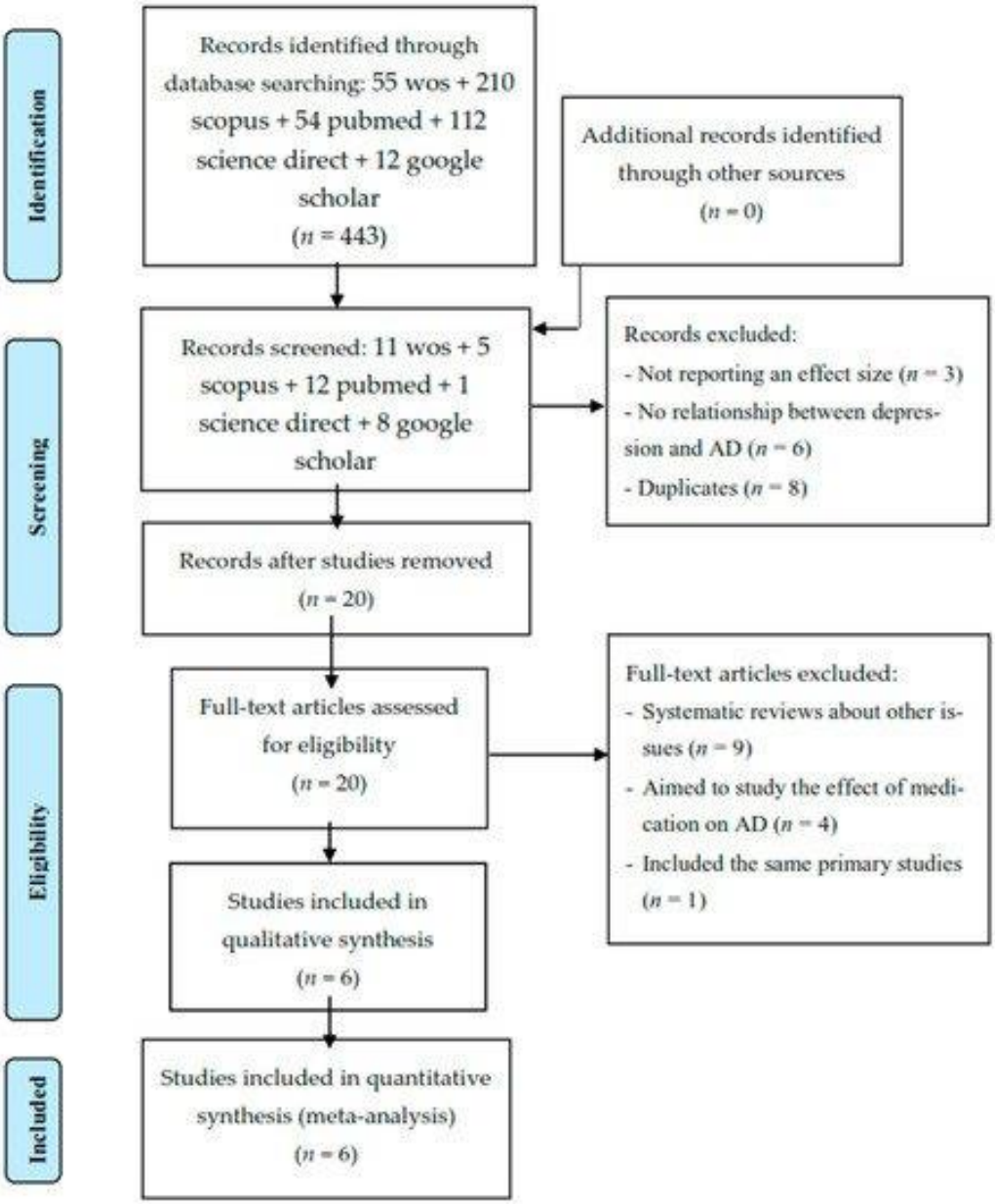

Figura 4. Flow chart depicting the selection of articles for our meta-analysis. Note: AD: alzheimer's disease; n: number of studies.

A total of 17 and 11 studies were based on symptomatic rating scales and clinical criteria to assess depression, respectively: CES-D (n = 14) (50%), DSM-III/III-R/IV/V (n = 8) (28.6%), GMS-AGECAT (n = 3) (10.7%), GDS (n = 2) (7.1%), and HAM-D (n = 1) (3.6%). AD diagnosis was established based on the N-ADRDA (n = 17) (56.7%) or DSMIII-R/IV/V (n = 10) (33.3%), ICD10 (n = 2) (6.7%), and N-AIREN (n = 1) (3.3%) scales.

Risk estimates were pooled across the 28 studies. The random effect of the relationship between depression and AD was significant (*OR* = 2.46, 95% *CI* [1.81–3.35], $Z = 5.72$, $p < 0.001$). Figure 5 shows the forest plot of the effect sizes and their 95% *CI*. Heterogeneity across studies was substantial (*Q-value* = 284.53, *df* = 27, $I^2 = 90.51$, $p < 0.001$), suggesting the presence of potential moderators (Table 8).

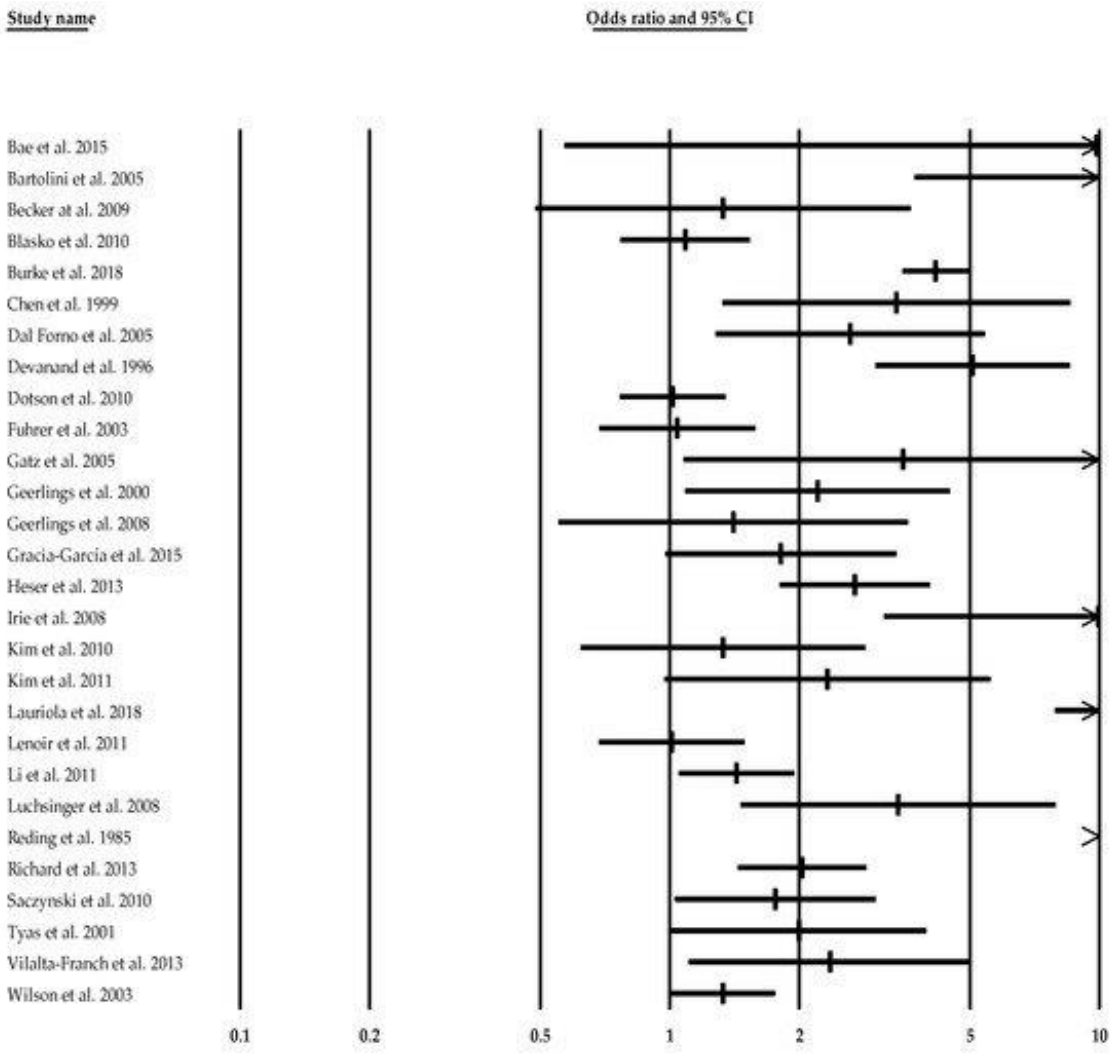

Figura 5. Forest plot of studies investigating the risk of Alzheimer's disease (Time2) associated with depression (including all instruments).

Tabla 8. Summary details for individual studies that examined the risk of dementia (OR) associated with depression.

	Odds Ratio	**Lower Limit**	**Upper Limit**	***Z-***	***p-***	**Cases (Depression**	**Controls (No Depression)**
Bae et al.	9.84	0.57	170.00	1.57	0.116	9/359	0/181
Bartolini et	16.00	3.72	68.76	3.73	<0.001	31/124	2/98
Becker at al.	1.33	0.49	3.65	0.56	0.578	*HR* = 1.33 (0.49–3.65)	
Blasko et al.	1.09	0.77	1.53	0.47	0.637	77/242	122/406
Burke et al.	4.15	3.49	4.94	15.98	<0.001	205/1214	507/10,869
Chen et al.	3.37	1.33	8.54	2.56	0.011	6/52	28/751
Dal Forno	2.63	1.28	5.40	2.63	0.008	*HR* = 2.63 (1.28–5.40)	
Devanand	5.07	3.02	8.52	6.13	<0.001	57/173	25/283
Dotson et	1.02	0.77	1.35	0.11	0.911	96/938	125/1239
Fuhrer et	1.04	0.69	1.58	0.19	0.849	30/203	196/1373
Gatz et al.	3.49	1.08	11.28	2.09	0.037	*OR* = 3.49 (1.08–11.28)	
Geerlings	2.21	1.09	4.48	2.20	0.028	*OR* = 2.21 (1.09–4.48)	
Geerlings	1.41	0.55	3.58	0.71	0.475	6/35	44/343
Gracia-	1.81	0.98	3.36	1.89	0.059	13/452	51/3174
Heser et al.	2.70	1.80	4.03	4.84	<0.001	34/306	118/2663
Irie et al.	9.94	3.16	31.22	3.93	<0.001	6/146	6/1397
Kim et al.	1.33	0.62	2.85	0.74	0.463	*HR* = 1.33(0.62–2.85)	
Kim et al.	2.33	0.97	5.56	1.90	0.057	7/45	38/518
Lauriola et	130.73	7.90	2162.50	3.40	0.001	57/115	0/66
Lenoir et	1.01	0.69	1.49	0.05	0.960	*HR* = 1.0 (0.7–1.6)	
Li et al.	1.43	1.05	1.94	2.28	0.022	*HR* = 1.43 (1,05–1,94)	
Luchsinger	3.40	1.46	7.90	2.85	0.004	*HR* = 3.4 (1.5–8.1)	
Reding et	19.00	12.42	29.06	13.59	<0.001	*HR* = 19.00 (12.40–27.90)	
Richard et	2.03	1.44	2.86	4.06	<0.001	55/452	109/1708
Saczynski	1.76	1.03	3.01	2.07	0.039	*HR* = 1.76 (1.03–3.01)	
Tyas et al.	2.00	1.01	3.95	2.00	0.046	21/36	271/658
Vilalta-	2.36	1.11	5.03	2.23	0.026	13/116	17/335
Wilson et	1.33	1.01	1.76	2.01	0.044	*OR* = 1.33 (1.01–1.76)	
Random	2.46	1.81	3.35	5.72	<0.001		

Note: AD: Alzheimer's disease; NO-AD: No Alzheimer's disease. Ns are based on total participant data available for de- pression or AD (not entire sample). Some data (N at baseline and follow-up) were not available for the depression and control groups, because studies did not provide them. In those cases, we reported the effect given in primary studies. OR: odds ratio; LL: Lower Limit; UL: Upper Llimit; Z: standard punctuation; p: statistical significance

II. Clinical Criteria and Symptomatic Rating Scales to Assess Depression

We tested three different models that reflected a combination of methodological moderators (see Table 9). Random effect models revealed a significant positive effect size of the association between depression and risk of AD for clinical (k = 11) and symptomatic (k = 17) measures of depression. Heterogeneity was substantial for the depression criteria (I^2 = 90.51), indicating that the *OR* was greater for clinical than symptomatic measures.

Tabla 9. Summary effect sizes.

		Model Statistics						
		OR	***LL***	***UL***	***Z***	***p***	**Weight Random**	***Std* Residual**
Depression criteria (model 1)								
Clinic	11	3.68	2.44	5.55	6.20	0.0001	172.78 ***	6.86 **
Symptomatic	17	1.81	1.30	2.53	3.51	0.0001		
Depression scale (model 2)								
GDS	2	1.63	0.64	4.15	1.03	0.303		
CES-D	14	1.60	1.28	2.02	4.07	0.0001	37.83 ***	1.87
HSRD	1	3.40	1.19	9.71	2.29	0.022		
Cut-off (CES-D) (model 3)								
≥4	2	1.63	0.97	2.78	1.80	0.072		
≥10	3	2.02	1.14	3.60	2.39	0.017	28.63 **	1.97
≥16	8	1.44	1.04	2.00	2.19	0.028		
≥20	1	2.63	0.97	7.11	1.91	0.057		

Note: *** $p \leq 0.001$, ** $p \leq 0.01$, k: number of studies; OR: Odds ratio; LL: Lower limit; UL: Upper limit; Q_w: heterogeneity within; Q_b: heterogeneity between.

Then, we performed an additional sub-group analysis distinguishing between types of symptomatic rating scale used to assess depression. The total effect (*OR*) was significant (1.80, 95% *CI*: 1.16–2.78, $Z = 2.62$, $p = 0.009$), and heterogeneity was moderate ($I^2 = 61.84$). Sub-group analysis yielded a significant effect of depression on the development of AD for studies using the CES-D scales and HSRD, although this effect was non-significant when studies used the GDS scale. Only one study included the HSRD scale, and no additional subsample analyses were conducted. However, sufficient data were available for the CES-D ($k = 14$). We conducted further sub-analyses according to different cut-off points of the CES-D scale to define presence of depression. *ORs* were pooled across 14 studies (*OR* = 1.68, *IC* 95% 1.24–2.27, $Z = 3.36$, $p = 0.001$). Heterogeneity was moderate across these studies ($I^2 = 63.95$), indicating that the effect of depression on the risk of AD may differ according to the cut-off points used. Estimates were significant for ≥10 and ≥16 cut-offs,

whereas the effect of depression on AD was not significant when studies used a cut-off of ≥4 and ≥20 (Table 9).

III. Meta Regression Analysis

We conducted a meta-regression analysis to determine whether the criteria used to measure depression might explain differences across studies in reporting effect size and might also cause heterogeneity. A significant negative effect of the use of symptomatic rating scales on the prediction of AD was found ($b = -0.71$, $Se = 0.27$, 95% *CI*: −1.24/−0.17, $Z = -2.59$, $p = 0.009$) compared to clinical criteria ($k = 28$, intercept: $b = 1.30$, $Se = 0.21$, CI: 0.89/1.72, $Z = 6.14$, $p \leq 0.001$) ($Q = 6.71$, $df = 1$, $p = 0.009$). Together, these explained 26% of the variance. That is, the use of symptomatic rating scales to assess depression was associated with a decreased likelihood of developing AD in the follow-up compared to the use of clinical criteria.

No significant moderating effects were found in meta-regression analyses conducted for the various symptomatic rating scales of depression ($k = 17$) (1 = GDS, intercept: $b = 0.47$, $Se = 0.45$ (−0.41/1.36), $Z = 1.04$, $p = 0.296$; 2. CES-D: $b = -0.02$, $Se = 0.46$ (−0.93/0.89), $Z = -0.04$, $p = 0.97$; 3. HSRD: $b = 0.75$, $Se = 0.68$ (−0.59/2.09), $Z = 1.10$, $p = 0.270$) ($Q = 2.18$, $df = 2$, $p = 0.336$). Differences explained the 28% of variation observed in the association between depression and AD.

When analyzing the differential effect of the CES-D cut-offs on the development of AD ($k = 14$), results showed a greater predictive effect for studies using more restrictive cut-off points (≥20) (intercept: $b = 0.97$, $Se = 0.37$, 95% *CI*: 0.25/1.69, $Z = 2.63$, $p = 0.008$) (≥4: $b = -0.51$, $Se = 0.38$ (−1.26/0.24), $Z = 1.34$, $p = 0.180$; ≥0.10: $b = -0.50$, $Se = 0.39$ (−1.27/0.28), $Z = -1.26$, $p = 0.209$; ≥0.16: $b = -0.77$, $Se = 0.38$ (−1.51/−0.01), $Z = -2.04$, $p = 0.041$) ($Q = 7.43$, $df = 3$, $p = 0.050$]. The different cut-off points of the CES-D explained the 53% of variation in the diagnosis of AD (Figure 6).

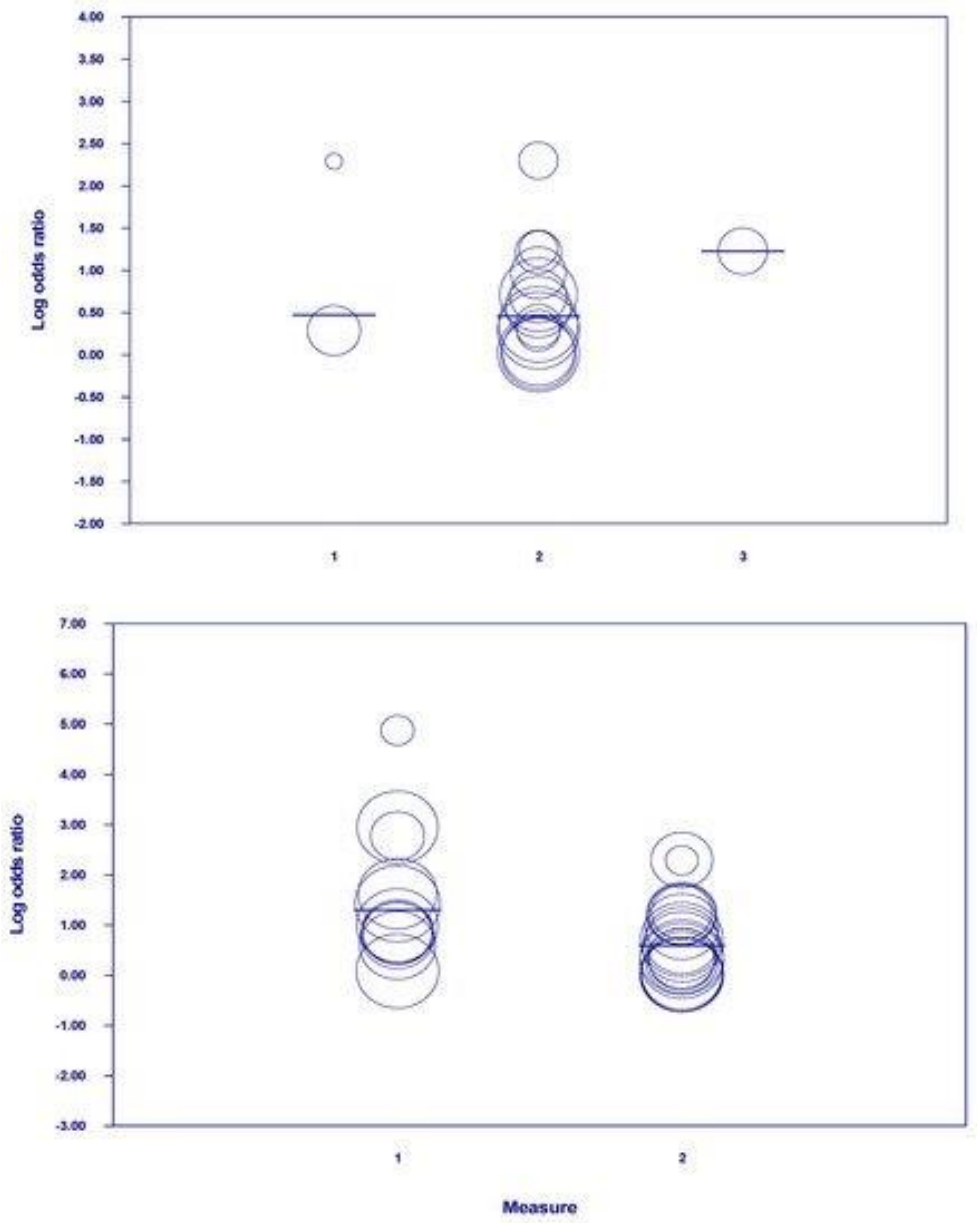

Figura 6. Plot of variation in the diagnosis of AD

DISCUSSION

The main contribution of this study was to produce precise AD risk estimates associated with different depression criteria, either clinically significant or based on symptomatic scales. Based on the results of 11 cohorts, we found a more than three-fold increased risk of AD for clinically significant depression. Likewise, based on findings of 17 cohort studies, the risk of AD increased almost two-fold in participants diagnosed with symptomatic measures of depression. We found that studies that used clinically significant criteria for diagnosis of

depression had more consistent and significant results than those that used symptomatic scales.

However, most included studies used self-reported symptomatic scales for diagnosis of depression, specifically the CES-D. We further analyzed the differential effect of CES-D cut-off points on AD risk and found that they explained 53% of the variability of results. We found a slightly significant predictive effect in meta-analyzed data of studies using the cut-off CES-D point ≥10 and ≥16, but predictive risk of AD was greater for one study using a more restrictive cut-off point (≥20). Our results are consistent with those of Cherbuin et al. (35) who found that the meta-analysis of studies using a cut-off previously validated against clinical criteria (≥20) demonstrated higher risk estimates than those using a more lenient cut-off (≥16).

We found a greater effect of clinically significant depression on AD risk than the MA of Santabárbara et al. (33), probably because that meta-study included only three studies with homogeneous criteria for the diagnosis of depression (GMS-AGECAT). We also included eight studies using DSM criteria for depression; all of them but one, Blasko et al. (149), found consistently higher risk of AD compared to any other criteria. However, some of them found relatively large (148,167) or even extreme values of *OR* (163).

Furthermore, our study includes recent references (34), and it did not analyze data from studies of patient groups with mixed psychiatric histories or all types of dementia. Even though the meta-analysis of Kuring et al. (34) analyzed 36 independent studies for all types of dementia, they only pooled $k = 8$ studies for AD (OR = 2.23). This inclusion criterion may explain why our results show a greater OR risk from depression to AD than previous meta-analyses (33–37). Furthermore, they did not analyze variability arising from the type of measure (clinical or symptomatic criteria) and from cut-off points used to assess depression across studies. Another strength of our study is that it includes a selection of prospective

cohort studies to provide more evidence in establishing the cause and effect, and the relationship between depression and AD (33). We analyzed a long follow-up period (4.9 years, range 1–23.6 years) to observe the potential association between depression (as an antecedent) and risk of AD, avoiding cross-sectional studies (34,35). This analysis covers a gap in the previous literature, adding new information about the association between depression and AD. Finally, previous meta-analyses limited the literature search to biomedical databases. In our study, we included five databases in order to provide coverage of publications from different countries, reducing the likelihood of publication bias (36,37).

Overall, our study is the first to review all previously available meta-analyses of depression as a risk factor of incident AD systematically. Moreover, we included individual studies when they assessed clinically significant depression or a validated cut-off score in a symptomatic depression scale, and we conducted differential meta-analysis of specific AD risk estimates according to depression criteria. Our study demonstrates how depression criteria can explain variability between studies in the association between depression and incident AD. We agree with Cherbuin et al. (35) about the importance of using objective and specific measures of risk in evidence-based clinical practice.

Several different hypotheses on the association between depression and dementia were suggested, yet the ways in which depression influences AD are yet unclear. For instance, antidepressant use (i.e., anticholinergic drugs) was shown to be associated with an increased risk of dementia (64–67). Furthermore, the ε4 allele of apolipoprotein E (APOE) was associated with the development of AD (160,161). However, the idea that ε4 and dementia may be linked has little support (183–186). In this vein, some risk factors, such as brain-vascular (187), cortisol, hippocampal atrophy (188), and neuroinflammation, could involve a possible common pathway to explain the association between depression and AD (189).

We should also recognize some limitations of our study. Firstly, as the studies included in the meta-analyses reported either the odds ratio or the hazard ratio for the association between late-life depression and dementia, we calculated the pooled *OR* for the association between depression and AD separately. Odds ratio is a measure of association between two conditions (such as in logistic regression models), whereas the hazard ratio is a measure of the strength of the association between two conditions in time-to-event statistical analysis. Given this, we should interpret the results from the pooled risk analysis with caution, as we included studies that reported hazard ratios and odds ratios together. Nonetheless, the results are very consistent across all analyses for AD. Secondly, individual studies assessing depressive symptoms by self-rating scales used pre-established cut-off scores, and no structured interviews were conducted for the diagnosis of depressive disorders, which may have introduced significant heterogeneity into the classification of cases and non-cases, in particular in individuals with mild depression; according our results, this may explain a good deal of the variability in results between studies. In addition, some of the studies included in this meta-analysis were not representative of the entire population (such as studies including only men) (160). Although we did not find a moderator effect of observation time (results not shown), and the results support the hypothesis that clinical depression is a risk factor for later development of AD, the influence of prodromal symptoms should not be discounted, and it remains to be determined. Furthermore, we did not examine the influence of any single study on the overall risk estimates with sensitive analysis that omitted them one by one. Moreover, by choosing to include studies that allowed us to calculate crude *ORs*, we implicitly included studies that provided estimates of the relation between depression and AD risk in the form of unadjusted *ORs*, so other study-related factors may have affected the outcomes of these studies (age or sex). Inclusion of these studies may have biased our results. Another possible limitation of this meta-analysis is that our search was limited to certain databases. We did a careful review of all references in potentially relevant publications, previous meta-

analyses, and systematic reviews published on depression and AD. Nevertheless, a search of other international databases (such as EMBASE and PsycINFO) might have led to the identification of additional studies that could have been included in this meta-analysis.

CONCLUSIONS

Although we cannot yet assert an etiological basis of the association, our study provides consistent data pointing to an increased risk of AD for clinically significant depression. Our findings highlight the importance of using more stringent and objective measures of depression in future studies. Depression should be assessed by clinicians with standardized, validated measures, and preventive strategies targeting at-risk individuals should be designed. Further studies need to assess the potential for treatment of clinically significant depression to decrease the risk of AD.

CAPÍTULO 4

"Detrás de esos ojos que ya no miran, y del silencio de tus labios, hay una vida".

Rita Gómez

Sáiz-Vázquez O, Puente-Martínez A, Pacheco-Bonrostro J, Ubillos-Landa S. Blood pressure and Alzheimer's disease: a review of meta-analysis. Front Neurol. 2023; 13. https://doi.org/10.3389/fneur.2022.1065335

CAPÍTULO 4: BLOOD PRESSURE AND ALZHEIMER'S DISEASE: A REVIEW OF META-ANALYSIS

ABSTRACT

Background: AD is a neurological disorder of unknown cause in which the death of brain cells occurs. Identifying some of the modifiable risk factors for AD could be crucial for primary prevention and could lead to reduce the incidence of AD. Objective: We aimed to perform a meta-meta-analysis of studies to assess the effect of blood pressure on diagnosis of AD.

Methods: The search was restricted to meta-analyses assessing high systolic and diastolic blood pressure and Alzheimer's disease. We applied the PRISMA guidelines.

Results: High SBP is associated with AD. The exploration of parameters (sex, age, study design, region, and BP measurements) shows that only region significantly moderates the relationship between BP and AD. Asian people are those whose SBP levels > 140 mmHg are associated with AD. BP is associated with AD in both people ≤65 and ≥65 and in cross-sectional and longitudinal studies. In the case of DBP, only in women is it associated with a higher risk of AD, particularly when DBP levels > 90.

Conclusions: SBP is associated with both cerebrovascular disease and AD. Therefore, future studies should use other uncontrolled factors, such as cardiovascular diseases, diabetes, and stroke to explain the relationship between SBP and AD.

Keywords: Alzheimer Disease, Blood Pressure, Diastolic Pressure, Systolic Pressure, Risk Factors, Meta-Analysis

INTRODUCTION

Worldwide, 55 million people are affected by dementia (190). Alzheimer is the most common cause of dementia, accounting for up to 75% of all dementia cases (191). The prevalence of Alzheimer's disease (AD) increases every year in individuals between the ages of 65 and 85 (192), and by the year 2050, the worldwide prevalence of Alzheimer's will grow fourfold, to 106.8 million (range 47.2-221.2) (193). While between the ages of 65 and 74, about 10 percent of people have AD, in those over 85, the risk increases by 50 percent (192). According to estimates by the World Health Organization (WHO), the projected global prevalence of AD by 2050 will increase 110 percent from 2010 (194).

AD is a neurological disorder of unknown cause in which the death of brain cells occurs (192). AD is the most common cause of cognitive impairment (195). AD is characterized by hallmark pathological changes such as extracellular Aβ plaques and intracellular neurofibrillary pathology, which selectively affect specific subclasses of neurons and brain circuits. While dementia is a general term, Alzheimer's disease is a specific brain disease. It is marked by symptoms of dementia that gradually get worse over time (196). Dementia is a rather broad syndrome of global cognitive decline. However, AD first affects the part of the brain associated with specific cognitive functions such as language (aphasia), motor skills (apraxia) and perception (agnosia) (197,198). Moreover, in AD early symptoms often include changes in memory, thinking and reasoning skills (199).

Some of the first symptoms that occur with AD (neuropsychiatric) are a direct cause of early institutionalization (200). In AD there is an identity loss (201) and worsening in the physical and social areas (200), along with the progressive deterioration of basic cognitive (episodic memory, linguistic and spatial orienting) and executive functions (inhibitory abilities and the visuospatial functions) (202). Emotional and mental health problems delusions and hallucinations, abnormal behaviors or physical violence and hitting) are common, cause

distress to caregivers, and may be amenable to treatment (203,204). All these symptoms affect the quality of life and activities of daily living in individuals diagnosed with this disease (204).

The most important non-modifiable risk factor for developing AD is age. The prevalence of Alzheimer's disease (AD) increases every year in individuals between the ages of 65 and 85 (192), and by the year 2050, the worldwide prevalence of Alzheimer's will grow fourfold, to 106.8 million (range 47.2-221.2) (193). While between the ages of 65 and 74, about 10 percent of people have AD, in those over 85, the risk increases by 50 percent (192). Many cardiovascular risk factors increase with age, such as high blood pressure, which moreover could affect the mechanisms that lead to impairment in the brain (205).

According to Ballard et al. (206), there are not only genetic factors associated with the development of dementia but also acquired factors (i.e., hypertension) that could predict a higher risk of AD. In this study, we particularly focused on analyzing high blood pressure (BP) as a risk factor for the development of AD (120,207). The overall prevalence of high BP in adults is 25%, with more than 50% of those individuals over 60 years of age (208). Vascular risk factors like BP could change the anatomy of the human body by modifying vascular walls or causing ischemia and cerebral hypoxia, which may consequently lead to the development of AD (209). Furthermore, BP could generate dysfunction in the blood-brain barrier, which has been associated with the genesis of AD (60). Studies on the relation between BP and Alzheimer's disease have yielded inconsistent results, showing an association between AD and high BP, or no significant associations between these variables (210–212). For example, Mielke found that systolic hypertension was associated with an increased risk of AD. However, they did not find an association between diastolic hypertension and AD (60).

Findings also established that the association between AD and hypertension was determined by age of onset (early <=65 and late >=65 onset AD). In fact, AD has been classified as presenile or early-onset (<=65) and as senile or late-onset (>=65) that tend to be sporadic and slow-moving (213). However, it is still not clear in the current literature whether age moderates the relationship between BP and AD. Indeed, some researchers have indicated that elevated BP occurring in both either middle age or late life may be involved in the development of AD (62,210,214). Also, one study concluded that high systolic BP (SBP) and diastolic BP (DBP) were related to worse cognitive function for persons aged 65 to 74. However, in older age (≥ 75), higher SBP and DBP were related to an adequate cognitive function (215).

Other studies have studied the relationship of hypertension to gender. Gillis and Sullivan (216). concluded that women are more likely to be prehypertensive than men. Furthermore, in the study by Anstey et al. (217) hypertension in middle age in women was associated with greater cognitive impairment and AD. However, recent studies have shown that the prevalence of hypertension is higher in men before the sixth decade of life, although it increases in women after menopause (218).

Related to regions due to the high incidence of hypertension in developed countries, studies are aimed at prevention strategies (219,220). In addition, the earlier onset and more aggressive development of the AD in the young population have been identified as risk factors for hypertension in these countries (221).

The literature refers to various degrees of hypertension. This study was based on the cut-off points established by International Society of Hypertension (ISH)(222). On the one hand, ISH establishes the following measures for SBP: Elevated (130-139 mmHg); Grade 1 (140-159 mmHg) and Grade 2 (160-179 mmHG). On the other hand, for DBP there are also three cut-off measurements: Elevated (85-89 mmHg); Grade 1 (90-99 mmHg) and

Grade 2 (100-109 mmHg) (222,223). Mielke et al. (224) concluded in their study that SBP measurements greater than 160 mmHg were associated with greater cognitive impairment in the elderly that may lead to AD. Likewise, in Launer et al. (210) elevated midlife SBP > 160 mmHg and DBP ≥ 90mmHg were particularly associated with an increased risk of AD.

Furthermore, longitudinal (37,170) and cross-sectional (225,226) studies have been used to identify risk factors and elucidate some characteristics of AD. To this end, we aggregated data of longitudinal and cross-sectional studies and used meta-analytic equation modeling to test for causal relationships. One major advantage of meta-analytic equations is that it allows an integration of the given data from all studies into one model and to specify models that have not been tested in the primary studies (227).

Based on the results and evidence of other articles and meta-analyses, we aimed to perform a meta-meta-analysis of longitudinal and cross-sectional studies to test the association between BP (high SBP and high DBP) and risk AD. We also aimed to pool findings separately from cross-sectional studies and longitudinal studies and to assess the effect of BP on the risk of subsequent diagnosis of AD.

MATERIALS AND METHODS

I. Data Collection

The search was restricted to meta-analyses assessing high SBP and DBP and AD. We applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (145). The literature searches were carried out in five electronic databases, including ISI Web of Science, Scopus, PubMed, Elsevier Science Direct, and Google Scholar. No publication date was set. The list of keywords was generated through a system of successive approximations: "blood pressure" and "Alzheimer's disease" and "meta-analysis." A Google Scholar search was also performed but limited to the title. The literature search was carried out in English and Spanish.

II. Criteria for inclusion in the study

The procedure applied to carry out this meta-meta-analysis was: 1) search and selection of meta-analyses assessing high SBP and DBP and AD; 2) selection of primary studies contained in the meta-analyses and the deletion of duplicates.

Meta-analyses and primary studies that met each of the following criteria were selected: (1) meta-analysis and primary studies that measured the relationship between hypertension (high SBP and DBP) and the risk of AD; (2) meta-analysis and primary studies reported data that allowed the estimation of a pooled effect size; (3) meta-analysis and primary studies that diagnosed AD through clinical examination, using defined diagnostic criteria, DSMV(198) and NINCDS-ADRDA(45); (4) meta-analysis and primary studies that reported the sample size; and (5) meta-analysis and primary studies written in English or Spanish.

To avoid bias in eligible studies, all abstracts were independently reviewed by two investigators (OS and AP). After excluding all irrelevant abstracts, the remaining articles were analyzed, and data precision was examined in detail. In meta-analysis where relevant data were lacking ($k = 1$), the authors were contacted to request additional data to be subsequently added to the meta-analysis. Then, duplicate reports were excluded to pool the primary studies. After all meta-analyses and primary studies were selected, a third researcher independently extracted the highlighted data (SU). Information on all data collected from the primary studies included in the meta-analysis is presented in appendix table. (Appendix 4: Table A3).

III. Quality assessment

The qualities of the meta-analyses were independently coded by two co-authors using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) tool (28), which has been shown to have good inter-rater agreement, reliability, and content validity (28,29). Total scores for the meta-analyses were calculated as the sum of the 11 items on a binary scale.

Quality classifications were set as low quality (0–4), moderate quality (5–8), and high quality (9–11).

IV. Statistical analysis

Initially, we reported the associations between hypertension and AD for each primary study included in the previous meta-analysis.

Then, for this review of meta-analyses, firstly, we calculated the cumulative incidence ratio (or Log risk ratio [LnRR]) of AD for both SBP and DBP for each primary study. Secondly, we identified separate effect sizes for SBP and DBP measurements and their relationships with the risk of AD. Thirdly, study outcomes were grouped according to the definition of BP (SBP or DBP) and the measurement of hypertension established by ISH: (1) SBP: Elevated (130-139 mmHg); Grade 1 (140-159 mmHg) and Grade 2 (160-179 mmHg). (2) DBP: Elevated (85-89 mmHg); Grade 1 (90-99 mmHg) and Grade 2 (100-109 mmHg) (222,223). Heterogeneity between study samples was assessed using Cochran's Q statistic (102). The I^2 statistic was calculated to express the fraction of variation between studies that was due to heterogeneity. The I^2 statistic explains the percentage of variance in the observed effects due to variance in the true effects. An I^2 value less than 25% was considered low heterogeneity, between 25% and 50% was considered moderate heterogeneity, and greater than 50% was considered high heterogeneity (102). Statistical significance was set at $p \leq 0.05$. Data were analyzed using Comprehensive Meta-Analysis Version 3.1 (Biostat Inc, NJ, USA) (103). Additionally, to test for the possibility of publication bias we computed the Egger regression test. Results revealed no evidence for a publication bias (229).

For each primary study included in the meta-analysis, we calculated the following (see Table 1): a) *k* or number of studies, b) effect size, c) 95% confidence interval of the effect, and d) *p* (two-tailed significance) (146). We used a random effect model for the calculation of pooled effect estimates. Then, to assess the heterogeneity of our results, subgroup analyses

were performed to examine the differential effects of type of BP: 1) SBP, 2) DBP and 3) BP (total) on the risk of AD. We did not assume a common among-study variance component across subgroups. High-resolution forest plots were also developed separately with random effects.

Additionally, moderating variables were selected on the basis of substantive considerations and the availability of data across studies included in the meta-analysis. We anticipated interstudy heterogeneity as there was some variation between studies according to the study design (longitudinal *k effect size* = 29 vs. cross-sectional *k effect size* = 46) and the measures of SBP (>140 mmHg *k effect size* = 52 and >160 mmHg *k effect size* = 8) and DBP (>85 mmHg *k effect size* = 2 and >90 mmHg *k effect size* = 9). Finally, we also considered whether age at exposure assessment (early age of onset ≤65 *k effect size* = 39, versus late age of onset or ≥65 *k effect size* = 36) could account for heterogeneity in associations. When possible, we used separate summary measures for early and late-life measures of blood pressure. Otherwise, blood pressure in early life or late life was defined according to the mean of age. Moreover, we also analyzed the sex (male or female) in the different blood pressure measurements. In the same line, we also analyzed the continent where the sample was recruited (Europe, Asia, and the North America) in the different blood pressure measurements.

RESULTS

A total of 214 studies were identified from major databases: 61 in ISI Web of Science, 55 in Scopus, 17 in PubMed, 79 in Elsevier Science Direct and 2 in Google Scholar. One hundred eighty-nine articles were excluded for inclusion in this review for various reasons: a) *k* = 89 were duplicates; b) *k* = 100 no information provided on the relationship between BP and AD.

Tabla 10. Characteristics of the population of the AD and BP studies

Study	Variable[1]	Design[2]	*K*[3]	Regions (*N*)[4]	Sample[5]	% F[6]	Age[7]	SBP/DBP[8] measure/mmHg	Results	Effect Size[9]			AMSTAR[10] scores
										Effect Size (RR)	95 % CI LL~UL	*p*	
Lennon et al.(60)	SBP	L (13-22)	6	EU (2), NA (2), AS (2)	AD *n* = 2208 HC *n* = 852683	47.3	M = 56.87	>140mmHg	>SBP > AD	1.18	1.02 ~ 1.35	0.021	10
								>160mmHg	>SBP > AD	1.25	1.06 ~ 1.47	0.006	
								>90mmHg	>DBP > AD[11]				
Xu et al.(43)	SBP	L (1-21)	39	EU (15), NA (20), AS (8), AF (1),	AD *n* = 21359 HC *n* = 1421593	50.5	M = 71.8	>140mmHg	> SBP > AD	0.87	0.70 ~ 1.0	0.000	10
	DBP		5		AD *n* = 743 HC *n* = 11653			>90mmHg	>DBP = AD	1.14	0.89 ~ 1.39	0.028	
Meng et al.(42)	SBP	L (10)	1	EU (1)	AD *n* = 79 HC *n* = 707	100	*M* = 45	>140mmHg	>SBP > AD	1.77	0.93 ~ 3.37	0.082	10
Guan et al.(15)	SBP DBP	L (2-27)	4	EU (2), NA (1), AS (1)	AD *n* = 176 HC *n* = 7283	56.3	40-92	>160mmHg >85mmHg	>SBP & DBP =AD	1.01	0.87 ~1.18	0.850	9
Wang et al.(46)	SBP	T	2	EU (1), NA (1)	AD n = 385 HC n = 3626	39	<65	>140mmHg >160mmHg	>SBP = AD	1.50	0.56 ~ 4.04	*0.036*	*10*
							≥ 65	>160mmHg	>SBP = AD	1.00	0.79 ~ 1.25	*0.180*	

Study	Variable[1]	Design[2]	*K*[3]	Regions (*N*)[4]	Sample[5]	% F[6]	Age[7]	SBP/DBP[8] measure/mmHg	Results	Effect Size[9]			AMSTAR[10] scores
										Effect Size (RR)	95 % CI LL~UL	*p*	
Wang et al.(46)	SBP						65-75	>160mmHg	>SBP = AD	1.01	0.66 ~ 1.53	0.215	
							75-85	>160mmHg	>SBP > AD	1.07	0.63 ~ 1.82	0.052	
	DBP		2	EU (1), NA (1)	AD *n* = 385 HC *n* = 3626		<65	>90mmHg	-	1.70	0.80 ~ 3.60	-	
							≥ 65	>90mmHg	>DBP = AD	0.75	0.43 ~ 1.32	0.066	
							65-75	>85mmHg	>DBP = AD	0.71	0.30 ~ 1.67	0.616	
							75-85	>90mmHg	>DBP = AD	0.52	0.32 ~ 0.85	0.267	

Notes:

[1] Variable: SBP: Systolic Blood Pressure; DBP: Diastolic Blood pressure. [2] Design: T: Cross sectional; L: Longitudinal. [3] *K*: Number of studies.[4] Regions: *N*: Number of independent studies. EU: European Union; NA: North America; AS: Asia; AF: Africa. [5] Sample: AD: Participants with Alzheimer Disease; HC: Health Control participants. [6] %F: Percentage of women. [7] *M*: mean of age. [8]Study outcomes were grouped according to the measurement of hypertension: (1) SBP > 140 mmHg and >160 mmHg, (2) DBP > 85 mmHg and 90 mmHg. [9] CI: 95% Confidence Interval; RR: Risk Ratio. LL: Lower limit; UL: Upper limit. [10] AMSTAR: Assessing the methodological quality of systematic reviews. https://amstar.ca/Amstar_Checklist.php. [11] Given that two studies used odds ratios and the others hazard ratios, the authors could not compute summary estimates.

Table 10 summarizes key features of the included primary diagnosis, design, number of primary studies, regions of origin of the study, sample size, gender, mean age, results, effect sizes of the relationships between BP and AD, and AMSTAR scores.

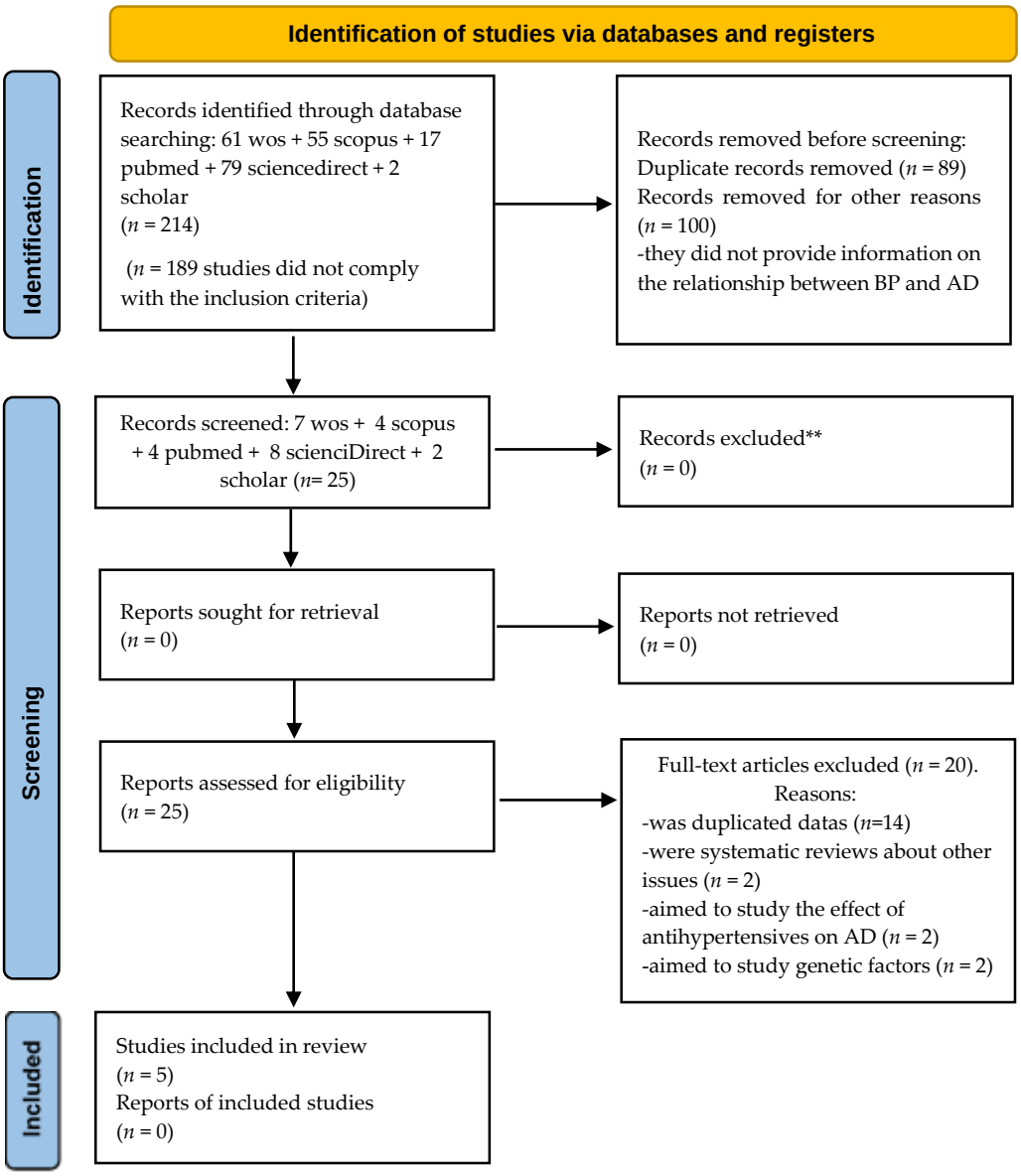

Figura 7. Flow chart depicting the selection of articles for our meta-analysis. Note: AD: alzheimer's disease; n: number of studies.

Although the meta-meta-analyses were based on the criteria established by ISH, the studies only showed values for the following cut-off points: SBP (>140mmHg and >160mmHg) and DBP (>85mmHg and >90mmHg). Eggers' test was not significant: the intercept (B0) is 0.47, se= 0.28, 95%CI (-0.09, 1.04), with t = 1.65, df. = 73, indicating no publication bias.

Twenty-five meta-analyses were eligible for inclusion in this review of meta-analyses. Of these meta-analysis, 20 meta-analyses were excluded because: a) *k* = 14 studies were duplicated data; b) *k* = 2 were systematic reviews about other issues; c) *k* = 2 aimed to study the effect of antihypertensives on AD; and d) *k* = 2 aimed to study genetic factors (Figure 7).

I. BP and AD: Heterogeneity analysis

Seventy-five effect sizes were extracted from a total of five meta-analyses that included *K* = 52 primary studies. Sixty effect sizes provided information about high SBP and risk of AD (80%); *k* = 11 about high DBP (14.7%); *k* = 4 about combined effect (5.3%). (Appendix 4: Table A3)

For the pooling LogRR analysis, we analyzed primary studies. The total effect size was Ln RR = 0.07, Se = 0.02 [0.031, 0.125], Z = 3.27, *p* = 0.001 and heterogeneity was high (Qb = 415.56, df = 74, *p* = 0.0000; I^2 = 82.19). These findings suggest that heterogeneity of effect may be present in some analyses.

II. Systolic blood pressure and AD

Four meta-analyses examined the relationship between high SBP and AD. The meta-analyses carried out by Lennon et al. (60) (*k* = 11 effect sizes; *N* = 7,666*; n* = 1,520 participants with AD and high SBP*; nHC* = 6,146 HC participants), Xu et al. (43) (*k* = 40 effect sizes; *N* = 1,443,213*; n* = 17,113 participants with AD and high SBP*; n* = 1,426,100 HC participants), Meng (42) (*k* = 1 effect size; *N* = 786; *n* = 79 participants with AD and high SBP; *n* = 707 HC participants), and Wang et al. (46) (*k* = *8* effect sizes; *N* = 5,885; *n* = 385 participants with AD and high SBP; *n* = *5*,500 HC participants) compared HC and AD subjects with high SBP. Only in two of them (42,60) found significant associations between high SBP and the risk of AD.

The total random effect of the high SBP value was (k = 60 effect sizes; N = 1,457,550 participants; *nAD* = 19,097 participants; *nHC* = 1,438,453) (Ln RR = 0.09, 95%CI = 0.013–0.166, Z = 2.28, p = 0.022) (see Table 11). The heterogeneity was high: Q-value= 380.08, df = 59, I^2 = 84.

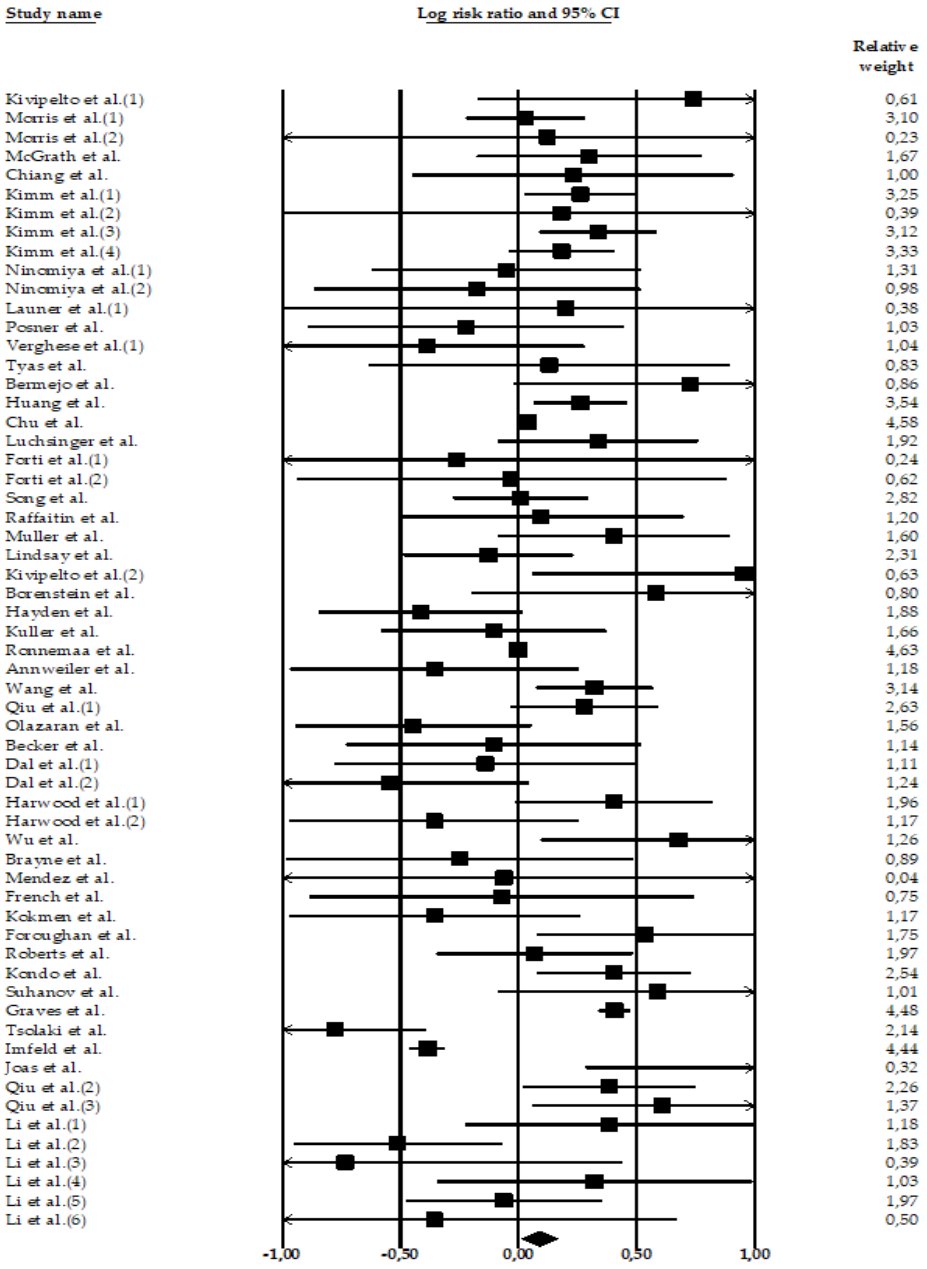

Figura 8. Forest plot of the meta-analysis of incidence rates of AD in participants withhigh SBP

Note: Individual and pooled estimates of the association between measures of hypertension and Alzheimer disease. The size of the box representing the point estimate for each study in the forest plot is proportional to the contributing weight of that study estimate to the summary estimate.

Tabla 11. Individual and pooled estimates of the association high SBP and AD.

Study name		Statistics for each study						
	Sample	*Lnog* RR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*
Lennon et al. (60)								
Kivipelto et al.(1) (120)	AD *n* = 48 HC *n* = 1400	0.74	0.47	0.22	-0.174	1.658	1.59	0.113
Morris et al.(1) (212)	AD n = 324 HC n = 378	0.03	0.13	0.02	-0.221	0.280	0.23	0.817
[1]Morris et al.(2) (212)	AD n = 54 HC n = 378	0.12	0.79	0.63	-1.430	1.674	0.15	0.877
McGrath et al. (230)	AD *n* = 81 HC *n* = 1440	0.30	0.24	0.06	-0.174	0.775	1.24	0.215
Chiang et al. (231)	AD *n* = 64 HC *n* = 292	0.23	0.35	0.12	-0.448	0.910	0.67	0.505
Kimm et al.(1) (232)	AD *n* = 282 HC *n* = 821	0.26	0.12	0.01	0.030	0.495	2.21	0.027
Kimm et al.(2) (232)	AD *n* = 164 HC *n* = 821	0.18	0.60	0.36	-1.000	1.364	0.30	0.762
[1]Kimm et al.(3) (232)	AD *n* = 274 HC *n* = 821	0.34	0.13	0.02	0.088	0.584	2.66	0.008

Study name		Statistics for each study						
	Sample	*Lnog* RR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*
[1]Kimm et al.(4) (232)	AD *n* = 206 HC *n* = 821	0.18	0.11	0.01	-0.041	0.405	1.60	0.109
Ninomiya et al.(1) (233)	AD *n* = 6 HC *n* = 149	-0.05	0.29	0.08	-0.619	0.516	-0.18	0.859
[1]Ninomiya et al.(2) (233)	AD *n* = 17 HC *n* = 177	-0.17	0.35	0.12	-0.865	0.516	-0.50	0.621
Total (60)		**0.20**	**0.06**	**0.00**	**0.090**	**0.307**	**3.58**	**0.000**
Xu et al. (43)								
Launer et al.(1) (210)	AD n = 81 HC n = 2.137	0.20	0.61	0.37	-0.996	1.394	0.33	0.744
Posner et al. (211)	AD *n* = 257 HC *n* = 1.259	-0.22	0.34	0.12	-0.892	0.446	-0.65	0.513
Verghese et al.(1) (234)	AD *n* = 65 HC *n* = 406	-0.39	0.34	0.11	-1.049	0.278	-1.14	0.255
Tyas et al. (170)	AD *n* = 35 HC *n* = 685	0.13	0.39	0.15	-0.634	0.897	0.34	0.737
Bermejo et al. (235)	AD *n* = 113 HC *n* = 3.824	0.73	0.38	0.15	-0.020	1.475	1.91	0.056

Study name		Statistics for each study						
	Sample	*Lnog* RR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*
Huang et al. (236)	AD *n* = 612 HC *n* = 142.744	0.26	0.10	0.01	0.064	0.460	2.60	0.009
Chu et al. (237)	AD *n* = 10 HC *n* = 153	0.04	0.02	0.00	0.009	0.069	2.54	0.011
Luchsinger et al. (166)	AD *n* = 246 HC *n* = 1.138	0.34	0.22	0.05	-0.087	0.760	1.56	0.120
Forti et al.(1) (238)	AD *n* = 18 HC *n* = 466	-0.26	0.77	0.60	-1.777	1.254	-0.34	0.735
Forti et al.(2) (238)	AD *n* = 30 HC *n* = 238	-0.03	0.46	0.21	-0.939	0.878	-0.07	0.948
Song et al. (239)	AD *n* = 416 HC *n* = 2.790	0.01	0.15	0.02	-0.276	0.296	0.07	0.946
Raffaitin et al. (240)	AD *n* = 134 HC *n* = 7.087	0.10	0.31	0.10	-0.509	0.700	0.31	0.757
Muller et al. (241)	AD *n* = 147 HC *n* = 1833	0.41	0.25	0.06	-0.085	0.896	1.62	0.105
Lindsay et al. (242)	AD *n* = 194 HC *n* = 4.088	-0.13	0.18	0.03	-0.486	0.231	-0.70	0.485

Study name		Statistics for each study						
	Sample	*Lnog* RR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*
Kivipelto et al.(1) (243)	AD *n* = 48 HC *n* = 1.449	0.96	0.46	0.21	0.060	1.851	2.09	0.037
Borenstein et al. (77)	AD *n* = 90 HC *n* = 1.859	0.58	0.40	0.16	-0.196	1.361	1.47	0.143
Hayden et al. (244)	AD *n* = 104 HC *n* = 3.264	-0.42	0.22	0.05	-0.847	0.016	-1.89	0.059
Kuller et al. (245)	AD *n* = 330 HC *n* = 2.807	-0.11	0.24	0.06	-0.582	0.372	-0.43	0.665
Ronnemaa et al. (246)	AD *n* = 127 HC *n* = 2.268	0.00	0.09	0.01	-0.182	0.182	0.00	1.000
Annweiler et al. (247)	AD *n* = 70 HC *n* = 498	-0.36	0.31	0.10	-0.968	0.254	-1.14	0.253
Wang et al. (248)	AD *n* = 8.488 HC *n* = 1.230.400	0.32	0.13	0.02	0.076	0.568	2.57	0.010
Qiu et al.(1) (249)	AD *n* = 333 HC *n* = 1.301	0.28	0.16	0.03	-0.034	0.590	1.74	0.081
Olazaran et al. (250)	AD *n* = 68 HC *n* = 1.376	-0.45	0.26	0.07	-0.946	0.054	-1.75	0.080

Study name		Statistics for each study						
	Sample	*Lnog* RR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*
Becker et al. (143)	AD *n* = 48 HC *n* = 288	-0.11	0.32	0.10	-0.729	0.518	-0.33	0.740
Dal et al.(1) (152)	AD *n* = 40 HC *n* = 576	-0.14	0.32	0.11	-0.775	0.496	-0.43	0.668
Dal et al.(2) (152)	AD *n* = 67 HC *n* = 781	-0.54	0.30	0.09	-1.134	0.045	-1.81	0.070
Harwood et al.(1) (251)	AD *n* = 202 HC *n* = 392	0.41	0.21	0.05	-0.011	0.822	1.91	0.056
Harwood et al.(2) (251)	AD *n* = 188 HC *n* = 84	-0.36	0.31	0.10	-0.969	0.256	-1.14	0.254
Wu et al. (252)	AD *n* = 201 HC *n* = 391	0.68	0.30	0.09	0.095	1.261	2.28	0.023
Brayne et al. (253)	AD *n* = 18 HC *n* = 340	-0.25	0.37	0.14	-0.983	0.486	-0.66	0.507
Mendez et al. (254)	AD *n* = 50 HC *n* = 407	-0.06	2.02	4.07	-4.015	3.891	-0.03	0.976
French et al. (255)	AD *n* = 76 HC *n* = 102	-0.07	0.42	0.17	-0.887	0.742	-0.17	0.861

Study name		Statistics for each study						
	Sample	*Lnog* RR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*
Kokmen et al. (256)	AD *n* = 203 HC *n* = 415	-0.36	0.31	0.10	-0.972	0.258	-1.14	0.256
Foroughan et al. (257)	AD *n* = 42 HC *n* = 115	0.54	0.23	0.05	0.078	0.995	2.30	0.022
Roberts et al. (258)	AD *n* = 151 HC *n* = 264	0.07	0.21	0.04	-0.348	0.483	0.32	0.750
Kondo et al. (259)	AD *n* = 60 HC *n* = 120	0.41	0.16	0.03	0.082	0.729	2.46	0.014
Suhanov et al. (260)	AD *n* = 127 HC *n* = 260	0.59	0.34	0.12	-0.086	1.262	1.71	0.087
Graves et al. (261)	AD *n* = 18 HC *n* = 340	0.43	0.03	0.01	0.339	0.472	11.90	0.000
Tsolaki et al. (262)	AD *n* = 65 HC *n* = 69	-0.77	0.19	3.86	-1.161	-0.391	-3.94	7.829
Imfeld et al. (263)	AD *n* = 3.541 HC *n* = 7.086	-0.38	3.75	1.41	-0.459	-0.312	-10.26	0.000
Total (43)		**0.05**	**0.05**	**0.00**	**-0.038**	**0.146**	**1.16**	**0.246**
Meng et al. (42)								

Study name		Statistics for each study						
	Sample	*Lnog* RR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*
Joas et al. (264)	AD *n* = 79 HC *n* = 707	1.59	0.67	0.45	0.285	2.902	2.39	0.017
Wang et al. (46)								
Qiu et al.(2) (265)	AD *n* = 150 HC *n* = 1.270	0.61	0.28	0.08	0.060	1.159	2.18	0.030
[1]Qiu et al.(3) (265)	AD *n* = 124 HC *n* = 441	0.39	0.19	0.03	0.019	0.751	2.06	0.039
Li et al.(1) (266)	AD *n* = 14 HC *n* = 530	0.39	0.31	0.10	-0.225	0.995	1.24	0.216
Li et al.(2) (266)	AD *n* = 19 HC *n* = 733	-0.51	0.23	0.05	-0.953	-0.069	-2.26	0.024
Li et al.(3) (266)	AD *n* = 37 HC *n* = 530	-0.73	0.60	0.36	-1.908	0.440	-1.23	0.220
[1]Li et al.(4) (266)	AD *n* = 31 HC *n* = 733	0.32	0.34	0.12	-0.346	0.990	0.95	0.345
Li et al.(5) (266)	AD *n* = 4 HC *n* = 733	-0.06	0.21	0.04	-0.476	0.352	-0.29	0.770
[1]Li et al.(6) (266)	AD *n* = 6 HC *n* = 530	-0.36	0.52	0.27	-1.384	0.670	-0.68	0.496
Total (46)		**0.08**	**0.16**	**0.03**	**-0.241**	**0.399**	**0.48**	**0.629**
Total random		**0.09**	**0.04**	**0.00**	**0.013**	**0.166**	**2.28**	**0.022**

[1] Measures SBP > 160. Lnog RR, natural log risk ratio; SE, estimator bias; VE, variance statistics; LLIC, Lower Limit confidence interval; ULIC, Upper Llimit confidence interval; Z, standard punctuation; p, statistical significance

III. Diastolic blood pressure and AD

Three meta-analyses showed the relationship between DBP and AD. Lennon et al. (60) (*k* = 1 effect size; *N* = 378; *n* = 78 with AD and high DBP; *n* = 300 HC participants), Xu et al. (43) (*k* = 5 effect sizes; *N* = 12,225; *n* = 497 with AD and high DBP; *n* = 11,728 HC participants). Wang et al. (46) (*k* = 5 effect sizes; *N* = 7,745; *n* = 306 with AD and high DBP; *n* = 7,439 HC participants). None of the three meta-analyses show significant associations between high DBP and AD.

Consistently, our results (*k* = 11 effect sizes; *N* = 20,348; *nAD* = 881; HC = 19,467) did not find an association between high DBP and the risk of AD (*LnRR* = 0.15, 95% *CI* = -0.045–0.338, *Z* = 1.50, *p* = 0.133) (see Table 12). The heterogeneity was high: *Q*-value=29.99, *df* = 10, I^2 = 66.65.

Tabla 12. Individual and pooled estimates of the association high DBP and AD.

Study name		Statistics for each study						
	Sample	*Log RR*	*Se*	*Ve*	*LLCI*	*ULIC*	*Z*	*p*
Lennon et al. (60)								
Morris et al.(3) (212)	AD *n* = 78 HC *n* = 300	0.44	0.49	0.24	-0.513	1.402	0.91	0.363
Xu et al. (43)								
Launer et al.(2) (210)	AD *n* = 87 HC *n* = 2.137	0.62	0.31	0.10	0.005	1.236	1.98	0.048
Verghese et al.(2) (234)	AD *n* = 65 HC *n* = 406	0.65	0.31	0.09	0.048	1.246	2.12	0.034
Qiu et al.(4) (249)	AD *n* = 87 HC *n* = 1.301	0.64	0.17	0.03	0.303	0.981	3.71	0.000
Ruitenberg et al. (267)	AD *n* = 107 HC *n* = 6.985	-0.11	0.11	0.01	-0.331	0.120	-0.92	0.359
Shah et al. (268)	AD *n* = 151 HC *n* = 899	0.00	0.01	0.00	-0.010	0.010	0.00	1.000

Study name		Statistics for each study						
	Sample	*Log RR*	*Se*	*Ve*	*LLCI*	*ULCI*	*Z*	*p*
Wang et al. (46)								
Qiu et al.(5) (265)	AD *n* = 245 HC *n* = 2249	-0.25	0.19	0.03	-0.613	0.116	-1.34	0.182
Li et al.(7) (266)	AD *n* = 22 HC *n* = 2.605	-0.20	0.53	0.28	-1.245	0.848	-0.37	0.710
Li et al.(8) (266)	AD *n* = 28 HC *n* =1.321	-0.31	0.39	0.15	-1.086	0.457	-0.80	0.424
[1]Li et al.(9) (266)	AD *n* = 4 HC *n* = 905	0.54	0.28	0.08	-0.018	1.091	1.90	0.058
[1]Li et al.(10) (266)	AD *n* = 7 HC *n* = 359	-0.04	0.22	0.05	-0.464	0.383	-0.19	0.850
Total random		**0.15**	**0.10**	**0.01**	**-0.045**	**0.338**	**1.50**	**0.133**

[1] Measures DBP > 90 Log RR, log risk ratio; SE, estimator bias; VE, variance statistics; LLIC, Lower Limit confidence interval; ULIC, Upper Llimit confidence interval; Z, standard punctuation; p, statistical significance

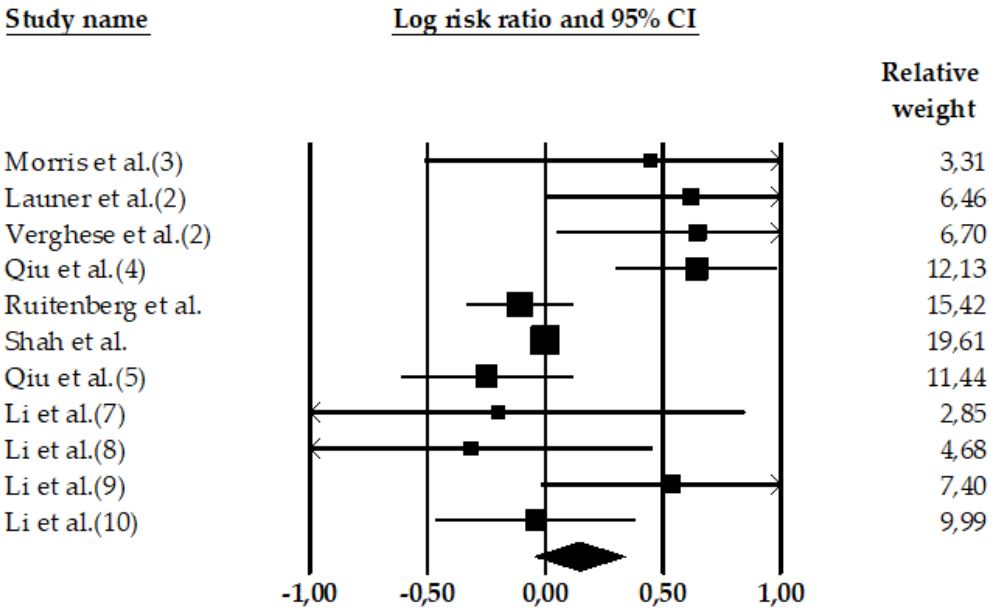

Figura 9. Forest plot of the meta-analysis of incidence rates of AD in participants with high DBP.

Note: Individual and pooled effect estimates of the association between diastolic BP hypertension (DBP) and Alzheimer disease. The size of the box representing the point estimate for each study in the forest plot is proportional to the contributing weight of that study estimate to the summary estimate.

IV. High DBP and High SBP Studies: Combined Effect Sizes

A meta-analysis reported a combined effect size for high SBP and high DBP (15). In this study (*k* = 4 effect sizes; *N* = 7,494; *n* = 211 with AD and high SBP/DBP; *n* = 7,283 HC participants) found a non-significant association between high SBP and high DBP and AD (*Ln*RR = 0.02, 95% *CI* = -0.179–0.222, *Z* = 0.21, *p* = 0.835) (see Table 13). The heterogeneity was medium: *Q*-value= 4.52, *df* = 3, I^2 = 33.69.

Tabla 13. Individual and pooled estimates of the association high BP and AD

Study name		Statistics for each study						
	Sample	*Log* RR	*Se*	*Ve*	*LLCI*	*ULCI*	*Z*	*p*
Guan et al. (15)								
Qiu et al.(6) (207)	AD *n* = 75 HC *n* = 719	0.22	0.20	0.04	-0.168	0.599	1.10	0.272
Stewart et al.(269)	AD *n* = 35 HC *n* = 1.778	-0.12	0.23	0.05	-0.566	0.333	-0.51	0.611
Treiber et al. (270)	AD *n* = 65 HC *n* = 3.634	0.17	0.14	0.02	-0.103	0.434	1.21	0.227
Hassing et al. (271)	AD *n* = 36 HC *n* = 1.152	-0.17	0.14	0.02	-0.441	0.092	-1.28	0.199
Total random		**0.02**	**0.10**	**0.01**	**-0.179**	**0.222**	**0.21**	**0.835**

Note: Log RR, log risk ratio; SE, estimator bias; VE, variance statistics; LLIC, Lower Limit confidence interval; ULIC, Upper Llimit confidence interval; Z, standard punctuation; p, statistical significance

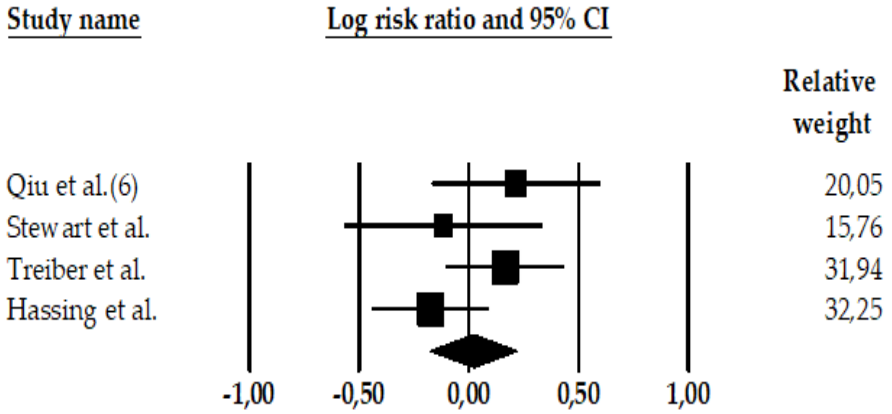

Figura 10. Forest plot of the meta-analysis of rates of AD in participants with high BP (high SBP and high DBP)

Note: The size of the box representing the point estimate for each study in the forest plot is proportional to the contributing weight of that study estimate to the summary estimate.

V. Subgroup analyses

Results of the subgroup analysis on the primary outcomes are presented in Table 5. Study outcomes were grouped by definition of hypertension and measures of blood pressure (e.g., SBP, DBP or total blood pressure). 60 effect sizes examined SBP at both grades (60): 52 effect sizes examined only grade 1 (>140 mmHg) (43,46) and 8 effect sizes examined only grade 2 (>160 mmHg) (15). Eleven effect sizes examined DBP at both grade: 2 effect sizes examined DBP using a cut off of > 85 mmHg (43,46) and 9 effect sizes > 90 mmHg. Four effect sizes combined both types of hypertension (15). Moderator analyses were performed comparing effect sizes according to sex (1: men and 2: women), age (1 age. ≤ 65 and 2. age ≥ 66), study design (1. cross-sectional or C and 2. longitudinal or L), and regions (1. Europe. 2. Asia and 3. North America).

Pooling studies that reported RRs for a total score of BP, results showed that sex, age and design did not moderate the relationship between hypertension and AD risk (Qb: $p \leq 0.50$). These results indicate that the risk of AD in participants with hypertension did not change significantly according to sex, age, and study designs groups. However, it can be observed that there are significant relationships between different categories of the variables sex, age and study design and AD (*Z*: $p \leq 0.50$. Findings revealed a significant relationship only between being women and a greater risk of AD ($p = 0.008$). Age was also associated with increased risk of AD in early ($p = 0.008$) and late age ($p = 0.047$) of onset, and this association was also significant in cross sectional ($p = 0.021$) and longitudinal ($p = 0.013$) studies. Regions moderated the association between BP and AD. The risk of AD was greater in studies that used samples from Asia and North America than those performed in Europe.

Results did not find significant differences in the risk of AD according to the measures of SBP (> 140 and > 160 mmHg) and DBP (> 85 and > 90 mmHg). Similarly, sex, age, design, and regions did not moderate the relationship between SBP and DBP and the risk of AD,

except sex in the case of DBP. Results found that women showed stronger risk of developing AD than men. It is also observed that only in longitudinal studies and Asia region, significant associations were found between SBP and AD.

According to measures of SBP (> 140 mmHg and > 160 mmHg), results indicated that SBP had no significant differences in effect sizes on the risk of AD at different sexes, ages, and designs. However, for SBP > 140 mmHg, there was evidence of heterogeneity between regions in RRs of AD. Asian countries showed stronger effect sizes between SBP and risk of AD than European and North American countries. Also, results found that elevated SBP (Systolic > 160 mmHg) was significantly associated with AD risk in the young elderly (≤ 65), longitudinal studies and in Europa and Asia.

For DBP (> 85 mmHg and > 90 mmHg), there was evidence of heterogeneity between sexes. Women with elevated DBP (>90 mmHg) showed a greater risk of AD than men. Furthermore, there were no significant differences in AD risk according to age, design, and regions.

Finally, age and regions did not moderate the relationship between combined effects of BP and the risk of AD.

Tabla 14. Effects of sex, age, design, and country in different types of SBP (>140 mm HG and >160 mm HG) and DBP (>80 mm HG and >90 mm HG)

		Statistics for each study								
	Effect sizes	*Log RR*	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*	I^2	*Qb*
BP (all types)										
Sex										
Men	54	0.06	0.04	0.00	-0.023	0.140	1.407	0.159	72.01	1.867, $p = 0.172$
Women	21	0.16	0.06	0.00	0.041	0.274	2.657	0.008	88.38	
Age										
≤65	36	0.09	0.03	0.00	0.024	0.160	2.645	0.008	58.70	0.280, $p = 0.596$
≥65	39	0.07	0.03	0.00	0.001	0.132	1.984	0.047	88.11	
Design										
C	46	0.06	0.03	0.00	0.010	0.120	2.303	0.021	87.61	0.744, $p = 0.389$
L	29	0.11	0.04	0.00	0.023	0.197	2.484	0.013	36.48	
Country										
Europe	23	-0.05	0.03	0.00	-0.113	0.025	-1.244	0.214	87.66	20.65, $p = 0.0001$
Asia	15	0.19	0.04	0.00	0.115	0.284	4.627	0.000	58.27	
North-America	37	0.11	0.04	0.00	0.038	0.190	2.939	0.003	62.02	

		Statistics for each study									
		Effect sizes	*Log* RR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*	*I2*	*Qb*
SBP											
>140		52	0.08	0.04	0.01	-0.007	0.158	1.786	0.074	86.01	0.948, $p = 0.330$
> 160		8	0.19	0.11	0.01	-0.027	0.407	1.720	0.085	3.14	
	Sex										
	Men	42	0.08	0.05	0.01	-0.015	0.174	1.649	0.099	67.99	0.107 $p = 0.744$
	Women	18	0.11	0.06	0.01	-0.012	0.221	1.158	0.079	88.94	
>140	Men	35	0.06	0.05	0.01	-0.045	0.162	1.11	0.267	71.87	0.237 $p = 0.626$
	Women	17	0.09	0.06	0.00	-0.025	0.222	1.565	0.118	89.81	
>160	Men	7	0.21	0.11	0.01	-0.009	0.426	1.880	0.060	15.65	0.018 $p = 0.895$
	Women	1	0.18	0.11	0.01	-0.041	0.405	1.601	0.109	0.000	
	Age										
	≤65	29	0.101	0.07	0.01	-0.034	0.250	1.495	0.135	54.50	0.133, $p = 0.715$
	≥65	31	0.07	0.07	0.01	-0.063	0.207	1.040	0.298	90.29	
>140	≤65	25	0.08	0.08	0.01	-0.084	0.234	0.927	0.354	49.01	0.000 $p = 0.987$
	≥65	27	0.08	0.07	0.01	-0.067	0.221	1.048	0.295	91.54	
>160	≤65	4	0.26	0.10	0.01	0.070	0.455	2.667	0.008	23.26	1.854

		Statistics for each study									
		Effect sizes	*Log* RR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*	*I2*	*Qb*
	≥65	4	0.01	0.17	0.03	-0.318	0.334	0.047	0.962	0.00	$p = 0.173$
	Design										
	C	41	0.06	0.05	0.01	-0.031	0.152	1.294	0.196	88.23	1.336 $p = 0.248$
	L	19	0.16	0.07	0.01	0.018	0.302	2.206	0.027	35.78	
>140	C	41	0.06	0.05	0.00	-0.032	0.152	1.290	0.198	88.23	0.517 $p = 0.472$
	L	11	0.14	0.10	0.01	-0.052	0.327	1.425	0.154	50.73	
>160	C	-	-	-	-	-	-	-	-		-
	L	8	0.21	0.07	0.01	0.065	0.356	2.834	0.005	3.14	
	Country										
	Europe	18	0.03	0.09	0.01	-0.148	0.198	0.284	0.777	89.30	5.785
	Asia	14	0.27	0.09	0.01	0.095	0.436	3.044	0.002	60.41	$p = 0.055$
	North-America	28	0.01	0.07	0.01	-0.130	0.152	0.156	0.876	64.11	
>140	Europe	17	0.00	0.09	0.01	-0.187	0.176	0.057	0.955	89.62	
	Asia	11	0.29	0.10	0.01	0.091	0.493	2.854	0.004	63.14	5.985 $p = 0.050$
	North-America	24	0.01	0.08	0.01	-0.143	0.160	0.109	0.913	67.66	
>160	Europe	1	0.61	0.28	0.08	0.060	1.159	2.176	0.030	0.00	

		Statistics for each study									
		Effect sizes	*Log* RR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*	*I2*	*Qb*
	Asia	3	0.23	0.08	0.01	0.067	0.389	2.771	0.006	9.15	3.562 $p = 0.169$
	North-America	4	0.01	0.17	0.03	-0.318	0.334	0.047	0.962	0.00	
DBP											
>80		2	0.21	0.24	0.06	-0.266	0.680	0.859	0.390	61.98	0.067 $p = 0.795$
>90		9	0.14	0.11	0.01	-0.081	0.358	1.236	0.217	69.65	
	Sex										
	Men	8	-0.01	0.06	0.01	-0.13	0.118	-0.109	0.913	39.20	13.37, $p = 0.0001$
	Women	3	0.62	0.15	0.03	0.307	0.927	3.897	0.0001	0.00	
>80	Men	2	0.22	0.29	0.08	-0.344	0.782	0.763	0.446	61.98	-
	Women	-	-	-	-	-	-	-	-	-	
>90	Men	6	-0.02	0.05	0.01	-0.126	0.079	-0.452	0.641	35.53	16.052 $p = 0.0001$
	Women	3	0.62	0.15	0.02	0.321	0.915	4.081	0.0001	0.00	
	Age										
	≤65	4	0.21	0.18	0.03	-0.133	0.552	1.198	0.231	85.01	0.131, $p = 0.717$
	≥65	7	0.12	0.16	0.03	-0.196	0.442	0.756	0.449	39.41	
>80	≤65	-	-	-	-	-	-	-	-	-	-

		Statistics for each study									
		Effect sizes	*Log* RR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*	*I2*	*Qb*
	≥65	2	0.22	0.29	0.08	-0.344	0.782	0.763	0.446	61.98	
>90	≤65	4	0.21	0.18	0.03	-0.147	0.574	1.160	0.246	85.01	0.245 $p = 0.621$
	≥65	5	0.08	0.21	0.04	-0.334	0.485	0.363	0.716	36.35	
	Design										
	C	5	0.26	0.14	0.02	-0.015	0.537	1.854	0.064	82.58	1.345, $p = 0.246$
	L	6	0.01	0.17	0.023	-0.317	0.334	0.052	0.958	28.15	
>80	C	-	-	-	-	-	-	-	-		-
	L	2	0.22	0.29	0.08	-0.344	0.782	0.763	0.446	61.98	
>90	C	5	0.26	0.14	0.02	-0.013	0.530	1.864	0.062	82.58	2.450 $p = 0.118$
	L	4	-0.15	0.21	0.05	-0.575	0.282	-0.671	0.502	0.00	
	Country										
	Europe	3	0.12	0.19	0.04	-0.253	0.498	0.638	0.523	87.13	
	Asia	-	-	-	-	-	-	-	-	-	0.074, $p = 0.786$
	North-America	8	0.19	0.15	0.02	-0.109	0.487	1.241	0.215	49.06	
>80	Europe	-	-	-	-	-	-	-	-	-	-
	Asia	-	-	-	-	-	-	-	-	-	

		Statistics for each study									
		Effect sizes	*Log* RR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*	*I2*	*Qb*
	North-America	2	0.22	0.29	0.08	-0.344	0.782	0.763	0.446	61.98	
>90	Europa	3	0.12	0.21	0.04	-0.278	0.525	0.604	0.546	87.13	
	Asia	-	-	-	-	-	-	-	-	-	0.041 $p = 0.840$
	North-America	6	0.18	0.19	0.04	-0.193	0.554	0.946	0.344	53.09	
BP (combined effects)											
	Sex										
	Men	4	0.02	0.10	0.01	-0.179	0.222	0.209	0.835	33.68	-
	Women	-	-	-	-	-	-	-	-	-	
	Age										
	≤65	3	-0.05	0.12	0.02	-0.289	0.192	-0.387	0.669	27.19	0.978, $p = 0.323$
	≥65	1	0.17	0.18	0.03	-0.182	0.513	0.934	0.350	0.00	
	Design										
	C										-
	L	2	0.02	0.10	0.01	-0.179	0.222	0.209	0.835	33.69	
	Country										
	Europe	2	-0.01	0.19	0.04	-0.383	0.383	-0.026	0.979	62.61	

	Statistics for each study									
	Effect sizes	*Log RR*	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*	*I2*	*Qb*
Asia	1	-0.12	0.32	0.10	-0.736	0.503	-0.368	0.713	0.00	0.522, $p = 0.770$
North-America	1	0.16	0.26	0.07	-0.339	0.670	0.643	0.520	0.00	

Note: Log RR, log risk ratio; SE, estimator bias; VE, variance statistics; LLIC, Lower Limit confidence interval; ULIC, Upper Llimit confidence interval; Z, standard punctuation; p, statistical significance; I2, heterogeneity; Qb, heterogeneity between

DISCUSSION

This study analyzes the association between high BP and the risk of AD. It is the first attempt to evaluate this relation through identifying previous meta-analyses and analyzing primary studies worldwide. The present study summarized the information on meta-analyses of hypertension (DBP and SBP) and AD and expands on findings from individual studies. In this study, fifty-two primary studies and seventy-five effect sizes were extracted. Furthermore, we included some moderator variables between high DBP and high SBP and AD such as sex, age, study design, regions, and measures of SBP and DBP.

Overall, results suggest that hypertension is associated with an increased risk of Alzheimer's disease (*RR* = 1.08, *IC* 95% [1.032, 1.13], $Z = 3.273$, $p = 0.001$). It indicates that the risk of AD increases 8% for patients with SBP.

In this study, forty-six primary studies and sixty effect sizes extracted from 4 meta-analysis (15,42,43,60) confirm the relationship between high SBP and AD (*RR* = 1.09, *IC* 95% [1.013, 1.181], $Z = 2.285$, $p = 0.022$). These results indicate that participants with high SBP increase the rate risk of AD by 9%, and support findings of previous studies which suggested that there were consistent demonstrations of a relationship between SBP and the risk of developing AD. In this vein, research demonstrated that high SBP could increase the risk of AD since it could cause neurobiological alterations (deposits of beta-amyloid protein), which lead to lesions in the brain, such as cerebral atrophy, formation of senile plaques and neurofibrillary tangles, which could be explanatory factors of the development of AD (272,273). Other studies also suggest that high SBP could cause brain vascular injury, leading to increase the flow of the blood, cerebral patency and cerebral amyloid angiopathy that were also associated with a higher risk of AD (274–276). However, our analysis cannot underlie the pathophysiology of AD and only could be defined SBP as a risk factor.

The relationship between high DBP and AD was studied through $k = 8$ primary studies and eleven effect sizes (3 meta-analyses) (43,46,60). Findings did not find a significant association between high DBP and the risk of AD. Nevertheless, according to previous studies these results could be explained by confounding due to associations between BP and advanced disease or to other unknown modifiable risk factors (277–279). For instance, secondary diseases such as obesity, cardiovascular diseases, silent infarcts, and vascular risk factors (280) or type 2 diabetes (272,277,278), could be closely related with the development of AD. Hence, in these cases it is not clear if hypertension is directly related to the risk of AD or whether AD is indirectly motivated for a secondary disease (279). Finally, there was a small number of studies analyzing DBP and AD in comparison with SBP, and in consequence, it is possible that we did not have sufficient statistical power to obtain a significant pooled estimate of the association between DBP and AD.

Related to the combined BP hypertension, only a meta-analysis (15) with four independent studies and effect sizes compared the incidence of AD between subjects with and without hypertension. These studies found that high BP is not associated with an increased risk of AD. This result is contradictory with the general view on the association between risk for AD and hypertension. For example, Guan et al. (15) points out that AD and hypertension are independent diseases with some common etiopathogenesis, which is a risk factor in AD.

To explore the influence of other research parameters in the relationship between high SBP and high DBP with AD, we analyzed different moderators: sex, age, study design and region. This study does not find differences in the risk of AD according to the type of measure of SBP (>140 and >160) and DBP (>85, >90). Total scores reveal significant differences between men ($RR = 0.99$, IC 95% [0.887, 1.125], $Z = -0.109$, $p = 0.913$) and women ($RR = 1.85$, IC 95% [1.359, 2.527], $Z = 3.897$, $p = 0.001$) (rate risk of AD increases by 85%), in the relationship of high DBP and AD, but not between SBP and AD. Specifically, the data

suggest that women with high DBP (> 90 mmHg) had an increased risk of AD compared with men (*RR* = 1.86, *IC* 95% [1.379, 2.498], *Z* = 16.05, *p* = 0.001), which increase the rate risk of AD by 86%. These results have been shown in previous studies that worked with different samples (women and men), where AD was also associated with high DBP mainly in women (276,277). For instance, Benetos et al. (281) found that DBP in women is associated with a higher cardiac output, pulse pressure and heart rate factors that are related with a higher risk of AD (63.8%).

Total scores of BP show that age is associated with increased risk of AD in early and late age of onset (*RR* = 1.10, *IC* 95% [1.024, 1.174], *Z* = 2.645, *p* = 0.008; *RR* = 1.07, IC 95% [1.001, 1.141], *Z* = 0.047, *p* = 0.047), in those results the rate risk of AD increase 10% and 7%. However, age of onset (≤65, early onset and ≥ 65 late onset) do not moderate the relationship between high SBP/DBP and AD showing similar effect sizes for both categories. Related to the measure of BP, this study found that elevated SBP > 160mmHg was associated with risk of AD in the young elderly (<=65), but not in those >= 65. In this vein, several studies have found that hypertension has different impacts on cognitive function at different ages (60,207,279). Current literature indicates that hypertension is a risk factor for cognitive decline in midlife and the young old age but may be protective against cognitive decline in late life (60). For example, some authors concluded that high BP in the early age of onset impacted cognitive functions and increased the risk of developing AD in older ages (207,282). Iadecola et al. (283) also found that hypertension in early onset is associated with higher risk of AD. Therefore, changes in blood pressure may be due to hemodynamic regulation being altered by neurodegenerative processes in the years preceding disease onset (60).

The only variable that moderates the relationship between BP and AD is the region. We observe higher risk of AD in Asia with SBP>140mmHg (*RR* = 1.34 *IC* 95% [1.096, 1.637],

Z = 2.854, p = 0.004) compared with European (*RR* = 0.99, *IC* 95% [0.829, 1.193], Z = -0.057, p = 0.955) and North America (*RR* = 1.01, *IC* 95% [0.866, 1.174], Z = 0.109, p = 0.913). Therefore, the rate risk of AD in Asia increases by 34%. These results are related with some studies. During the last four decades, the highest BP measurements worldwide have shifted from high-income countries to low-income countries, such as South Asia and Africa (284), which could explain our results (285,286). One the one hand, several authors suggest that recent lifestyle changes in Asia countries, such as diet, changing demographics, urbanization, environmental interactions, and other factors may help explain this relationship (286). On the other hand, one study with data from 90 countries showed that the percentage of people with hypertension receiving treatment increased in both high-income and low- and middle-income countries, but the gap between them widened (287). Moreover, our results also show that the risk of AD related to SBP>160mmHg in Europe (*RR* = 0.61, *IC* 95% [0.060, 1.159], Z = 2.176, p = 0.030) and Asia (*RR* = 0.23, *IC* 95% [0.067, 0.389], Z = 2.771, p = 0.006) are significant. However, in North America (*RR* = 0.01, *IC* 95% [-0.318, 0.334], Z = 0.047, p = 0.962) did not find a significant relationship. Despite these results, the strength of the association between SBP>160mmHg and AD risk is similar in the three regions.

Finally, results do not find differences in the effect size of the association between high SBP and DBP and the risk of AD according to the type of design (cross-sectional and longitudinal). Our results found an association between BP and the risk of AD in both types of studies. However, findings confirm that the relationship between higher SBP and AD is only significant in longitudinal studies and with SBP > 160mmHg (*RR* = 1.23, *IC* 95% [1.067, 1.428], Z = 2.834, p = 0.005), so the rate risk of AD increases by 23%, while high DBP (>85, > 90mmHg) is not related to an increased AD risk. In this vein, previous work found differences according to type of design that may result in part from the use of different definitions of hypertension and nonuniform measures of high or low BP. In this

study we use standardized criteria to define BP (SBP > 140/160mmHg and DBP > 85/90mmHg) and AD (clinical criteria) that could explain that there are no differences according to the study design. After controlling for this confounding factor, the effect size of longitudinal studies is higher in all the BP and SBP measures, although the differences do not reach significance. Longitudinal studies provide an opportunity to assess the temporal relation between BP and AD and the length of follow-up remains relevant since hypertension could render individuals more vulnerable to comorbid conditions such as cerebrovascular disease that confer greater risk for AD during long periods of follow-up.

However, our study is not without limitations. The key limitation is that only a small number of studies examined the association between DBP, both types of BP combined, and AD compromising the generalizability of the results. Furthermore, it is likely that due to the procedure used in this meta-meta-analysis some primary studies were not included. Another challenge was that studies reported outcomes using different metrics (*OR*, *HR* and *RR*). Likewise, not all the cut-off points established by ISH could be analyzed, since the stages of SBP ≥ 130-139 and DBP ≥ 100 could not be defined due to lack of primary studies. Other confounders may also influence the study's finding. For example, results were not adjusted for other risk variables including cardiovascular disease, stroke, alcohol consumption, smoking, kidney disease, and many others. Also, two studies did not report the mean of age of the sample, and they were not included in moderator analysis. Moreover, the relationship between hypertension and AD could not be thought of as binary but rather as a dynamic one, changing with life stage and disease state. Hence, a single measurement of BP may not accurately reflect the participant's average BP measurements. Additionally, data on the age at onset of hypertension and years of living with the condition may be important in clarifying temporal relationships between hypertension and AD. Also, we did not examine the potentially modifying impact of antihypertensive therapy on the relationship between hypertension and AD. In addition, another limitation is the absence of studies from South

America and Australia. Finally, we did not include educational level as a moderator variable since the external validity of some of results have been questioned. The primary studies contained in this meta-analysis used very different forms of measurement. For instance, some studies analyzed education using individual (i.e., no formal education, mandatory education, secondary studies, university studies) (250,257) or community-based samples (i.e., family education level, region or country) (257), quantitative (linear relation between the number of years of education and the risk of dementia) (152,252) or qualitative measures (a threshold effect at a given level of education) (255) and composite measures (i.e. socioeconomical status, SES defines education plus income) (239,288) that show different results. Therefore, we should interpret our results cautiously.

Several strengths of our review of meta-analysis should be emphasized. First, most prior studies were drawn from general community samples or non-Alzheimer's dementia-specific studies (vascular dementia, cortical dementia, or dementia in general) whereas the current study relied on Alzheimer's disease. Second, we add to the current literature analyzing fifty-two primary studies extracted from previous meta-analysis increasing the statistical power in our results. Third, we have analyzed the impact of different moderators (sex, age, study design, region, and measures of SBP/DBP) to explore the influence of other research parameters in the relationship between high SBP and DBP and AD. Finally, we want to focus on effect sizes since the statistical significance should never be interpreted as evidence that an effect had a clinical importance. It is important to note that the effect sizes were "relatively small" and the variation is great within the same meta-analysis. Therefore, the clinical significance and practical importance of these results should be considered in relation to the patient's status, goals, and clinician experience.

As a practical implication, this study suggests that high SBP could be a risk factor for AD. There is limited evidence that single cardiovascular risk factors affect AD risk, but the

strength of the association is influenced greatly by changing the parameters of the risk factors and in particular by identifying interactions between the factors. Future research should confirm this and determine whether stabilizing BP might be a target to slow decline the development of AD.

CONCLUSION

In summary, this study analyzes the association between SBP/DBP/combined BP and the risk of developing AD. A total of five meta-analyses and 52 primary studies were analyzed in this review of meta-analysis. Our study found that SBP is associated with increased risk of AD by 11%, although no association was found for DBP. Measures of SBP>140, SBP>160, DBP>85 and DBP>90 does not moderate the relationship between SBP and DBP and AD. Moderator analysis (sex, age, study design, region, and measures of SBP/DBP) show a significant association between high DBP (>90) and AD in women. The age of onset (<=65. early onset AD and. >= 65 late onset AD or senile AD) did not moderate the relationship between SBP and DBP and AD. Finally, regarding the type of study there were no differences in the association between BP y AD between longitudinal and cross-sectional studies. However, Asian countries showed stronger effect sizes between SBP > 140 and risk of AD than European and North American countries. Future work should use other uncontrolled factors (e.g., cardiovascular diseases, diabetes, and stroke) to explain the relationship between high BP and AD.

CAPÍTULO 5

"Un amigo es alguien que conoce la canción de tu corazón y puede cantarla cuando a ti ya se te haya olvidado la letra".

(Julio Ramón Ribeyro)

Sáiz-Vázquez O, Ubillos-Landa S, Puente-Martínez A, Pacheco-Bonrostro J. Systematic review of stroke and the risk of Alzheimer Disease. Eur Stroke J. 2023. (en revisión).

CAPÍTULO 5: A SYSTEMATIC REVIEW OF STROKE AND THE RISK OF ALZHEIMER DISEASE

ABSTRACT

Background: In recent years, several population-based studies have shown that the rate of cognitive decline is accelerated in people with a history of stroke. But the relation between stroke and AD is still an area of controversy. The current study examined the relationship between stroke and Alzheimer's disease (AD) analyzing previous literature.

Methods: We searched the literature in 5 databases and no initial publication date was set. We included longitudinal population-based studies examining the association between stroke and risk of AD. The meta-analysis was conducted using Comprehensive Meta-analysis 3.1

Results: Results report significant association between ischemic stroke (IS), hemorrhagic stroke (HS) and microinfarcts (MI) with the risk of AD. Even though results show heterogeneous effects between studies, this review did not found differences in the association between any type of stroke and AD according to age, sex or country.

Conclusion: Our study describes incidence rates of AD in patients with episodes of stroke (IS, HS and MI), and suggests that the risk of AD may be higher in patients that suffer stroke when compared to matched controls without incidence of stroke. Moreover, moderator analysis supports the robustness of our results.

Keywords: Alzheimer's disease; Stroke; Meta-analysis Ischemic Stroke; Hemorrhagic Stroke; Cerebral Infarction.

INTRODUCTION

Alzheimer disease (AD) is the most common dementing illness in the elderly(289). Over 13.8 million individuals with AD will be affected in 2050 (290). Mid-range estimates of net annual expected costs for an AD patient older than 70 years of age are over $81,000 and will reach $92,060 by 2030 (291). However, there is no effective treatment to cure AD or to inhibit the progression of AD symptoms (292). Therefore, urgent measures must be taken to reduce AD, considering that a condition with escalating costs and very limited treatment options.

Neurodegenerative diseases such as stroke and AD are two inter-related disorders that affect the neurons in the brain and central nervous system (293). Stroke is characterized as a neurological clinical sign of focal (or global) disturbance of cerebral function by a vascular cause, including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage, and is a major cause of disability and death worldwide (294). In fact, it is the second most common cause of death worldwide and it is on the top of high public health issues in the 21st century (295). Research estimate that one in 5 patients with stroke will end up demented shortly after a stroke (19). When a stroke occurs, a series of interconnected vascular and cerebral changes contribute to the progression towards cognitive impairment (296). Moreover, AD and stroke share some risk factors such as low education, sedentary lifestyle, and having at least one heart disease (297).

There are different types of strokes: ischemic stroke (IS), hemorrhagic stroke (HS) and microinfarcts (MI). IS is defined by the sudden loss of blood flow to an area of the brain with the resulting loss of neurologic function. It is caused by thrombosis or embolism that occludes a cerebral vessel supplying a specific area of the brain (298). Brain dysfunction caused by IS is often localized to the affected vascular territory (299). Hemorrhagic stroke (HS) is due to bleeding into the brain by the rupture of a blood vessel (300). The cause of

this increased stroke risk is multi-factorial. For example, chronic obstructive pulmonary disease may increase the risk of IS, whereas dialysis may increase the risk of HS (301). Cerebral MI are defined as microscopically demarcated regions of cellular necrosis that are not visible by macroscopic inspection of the brain (302). Despite being small lesions, affected individuals can have hundreds to thousands of cerebral microinfarcts, which is why they are associated with some dementias such as AD (303). No pharmacological treatment to date, however, has shown the qualities of restoring cognitive function or preventing further deterioration after stroke (296).

There are many theories that try to explain the association between AD and stroke. Firstly, the APOE ϵ4 allele is a genetic risk factor for AD with stroke (304,305). Secondly, brain imaging results suggest that intracerebral vascular dysregulation could be a cause for developing AD (306). This hypothesis is based on the presence of vascular risk factors that reduce cerebral blood flow to a critical threshold that decreases the supply of nutrients such as glucose and oxygen to the brain, essential for maintaining normal neuronal activity (307). Thirdly, beta amyloid (Aβ), a major component of senile plaque in AD, tend to appear after a stroke (308). Amyloid protein is associated with features – brain atrophy and progressive cognitive decline – that are typically considered hallmarks of neurodegenerative diseases such as AD (309).

Moreover, variables such as age, sex or country could also contribute to the development of AD and stroke. Research found that age is one of the strongest predictors for AD (310). Several studies suggest that patterns of brain gray matter atrophy may vary across the AD spectrum and depend on age and disease diagnosis (311,312). AD is commonly categorized as either early onset (EOAD) or late onset (LOAD) based on an age cutoff, typically 65 years. Early-onset AD includes a percentage of phenotypic variants that differ from the usual amnestic presentation of typical AD (313). AD affects 10-15% of individuals over 65

years and up to 47% of individuals over the age of 80 (314). Van Veluw et al. (303) find that hippocampal volume is independently affected by ageing and AD, such that the amount of hippocampal atrophy in young and elderly AD patients is similar. Nevertheless, the typical phenotype presentation of late-onset AD is characterized by predominant impairment of anterograde episodic memory, dysfunction in additional cognitive domains such as visuospatial, language, and executive function, eventually resulting in global cognitive decline, complete dependency, and death (315). On the other hand, Nakayama et al. (316) concluded that age was not related to stroke, however, age independently influences stroke outcome selectively in ADL-related aspects (BI) but not in neurological aspects (SSS), suggesting a poorer compensatory ability in elderly stroke patients. Kelly-Hayes et al. (317) demonstrated that the risk of stroke increased with age, with the incidence doubling with each decade after the age of 45 years, and more than 70% of all strokes occurring in persons aged 65 years or older.

Sex differences in risk of clinically diagnosed AD indicate that AD pathology is stronger in women (318). First, neuronal densities and estimates of the number of neurons are higher in men (319). Secondly, men and women with AD exhibit different cognitive and psychiatric symptoms, and women show faster cognitive decline (320). Thirdly, the prevalence and effects of cerebrovascular risk factors for AD are different between men and women, being higher in men (321). Increasing evidence suggests that sex differences exist in stroke. Moriel et al. (322) estimated, on the one hand, that the incidence of stroke is higher in men and, on the other hand, that there is a higher mortality rate in women than in men after stroke.

Additionally, research found differences between countries in the prevalence of AD. A previous study suggests that AD prevalence estimates in developing Asian and Latin American countries are high (≥5%), but consistently low (1–3%) in India and Sub-Saharan Africa (323). The lower prevalence in Africa and South Asia could be explained in part by a

lower survival of patients with dementia rather than lower incidence (324). In developed countries, the development of neurological diseases such as AD is related to aging of the population (325). Recent data in the study by Turana et al. (286) show also that the prevalence of AD is related to age in Asian countries. Nevertheless, in Latin America the higher rates of dementia and AD as one dementia's type may be due to issues of poverty, cultural barriers, and socioeconomic vulnerability (326). In addition, the highest estimated risks of stroke in different countries were: East Asia (38.8%), Central Europe (31.7%) and Eastern Europe (31.6%) (327). Epidemiological studies done in the USA, Europe, and Asia found that being overweight and obese was significantly associated with an increased incidence of IS, but the association with HS incidence was not always consistent (328).

The goal of this study was to perform a systematic review of available literature and conduct a meta-analysis of longitudinal primaries studies which reported incident stroke in AD patients. We estimated the risk of AD comparing patients that suffered an incident of stroke (IS, HI and MI) in a matched population without a previous history of stroke. Therefore, this study: a) estimates the effect size of the relationship between AD and stroke (IS, HS and MI), and b) analyzes whether this effect size varies as a function of different moderating variables (age, sex, country).

MATERIALS AND METHODS

I. Data Collection

In order to explore the association between different types of stroke (IS, HI and MI) with AD, we conducted a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (27). The PRISMA checklist is presented in the (Appendix 5: Table A4).

The search was carried out in 5 databases: ISI Web of Science (WoS), Scopus, PubMed, Elsevier Science Direct, and Google Scholar. No initial publication date was set. We used

some key search terms including "stroke", "microvascular infarcts", "ischemic stroke", "hemorrhagic stroke" and "meta-analysis" and "dementia" or "Alzheimer's disease". The search was limited to English language publications and studies of humans. A search date was not set. Searching in the Google Scholar database were limited to the title. We also reviewed the reference lists of relevant primary articles and reviews to identify studies that may have been missed in the search.

The search performed allows us to select longitudinal meta-analyses that meet the inclusion criteria. Subsequently, each of the primary studies included in the meta-analysis is reviewed to select only those that meet the inclusion criteria, since some of these studies focus on non-specific variables of the relationship between AD and stroke. The same criteria and procedures were used to select the meta-analyses and the primary studies included in these meta-analyses.

Finally, another search was conducted to check if there were any primary longitudinal studies not included in the meta-analyses. The search was conducted from the year 2017 to the present and no studies were located.

II. Criteria for inclusion in the study

Following criteria of many other meta-analyses in this field, the following inclusion criteria were established: (1) reported effect size; (2) longitudinal meta-analysis or primary studies measure the relationship between stroke and AD; (3) meta-analysis that provide sample data; (4) subjects without a diagnosis of AD at baseline; (5) AD was diagnosed by diagnostic criteria (DSM, ICD...); (6) meta-analysis score greater than 9 on AMSTAR; (7) studies should be controlled, with participants divided into the AD group and the control group.

Case reports, narrative reviews, letters, animal studies, articles in languages other than English and articles reporting data on the interaction of some types of drugs with stroke and AD were excluded.

III. Data extraction

Two authors (OS and AP) extracted key information of the studies according to a preplanned form, and recorded it in two separate databases, which were later compared and corrected for inconsistencies. When conflicts appeared in inclusion, exclusion, or data extraction, they were solved by discussion or the involvement of a third reviewer (SU). The following variables were collected: study, year, type of stroke (IS, HS and MI), population size (*N*), number of studies (K), country (ies), percentage of women (% F), age mean (*M*), main results of the study, effect sizes (Odds Ratio and 95% confidence limits) and AMSTAR scores. If studies reported different types of stroke were defined as effect size for every type.

For meta-analysis, we calculated the odds ratio (OR) of AD for every type of stroke. Study results were pooled by measures of every type of stroke (IS, HS and MI). We reported associations between stroke and AD for each primary study (Appendix 5: Table A5.) included in the above meta-analysis (Table 15).

Data were entered into Comprehensive Meta-Analysis version 3.1 (Biostat Inc, NJ, USA) (103). Heterogeneity between study samples was assessed using Cochran's Q statistic (329). The I^2 statistic was calculated to express the fraction of variation between studies that was due to heterogeneity (330). The I^2 statistic explains the percentage of variation in the observed effects due to the variation in the actual effects. An I^2 value less than 25% was considered low heterogeneity, between 25% and 50% was considered moderate heterogeneity, and more than 50% was considered high heterogeneity (102). Statistical significance was established at $p \leq 0.05$.

IV. Quality Assessment

To assess the quality of all included studies we used the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) tool (29), which has been shown to have good inter-rater agreement, reliability, and content validity (28). Total, scores for meta-analyses were

calculated as the sum of the 11 items on a binary scale. Quality ratings were established as low quality (0 to 4), moderate quality (5 to 8), and high quality (9 to 11).

RESULTS

A total of 448 meta-analysis were identified in the search: 68 in ISI Web of Science, 135 in Scopus, 49 in PubMed, 194 in Elsevier Science Direct, and 2 in Google Scholar. A total of 398 studies were removed before screening. Duplicate records (*n* = 67) and records removed for other reasons (*n* = 331): genetic studies (*n* = 87); not related with stroke (n = 92); relationship between dementia and stroke (*n* = 109); pharmacology studies (*n* = 43).

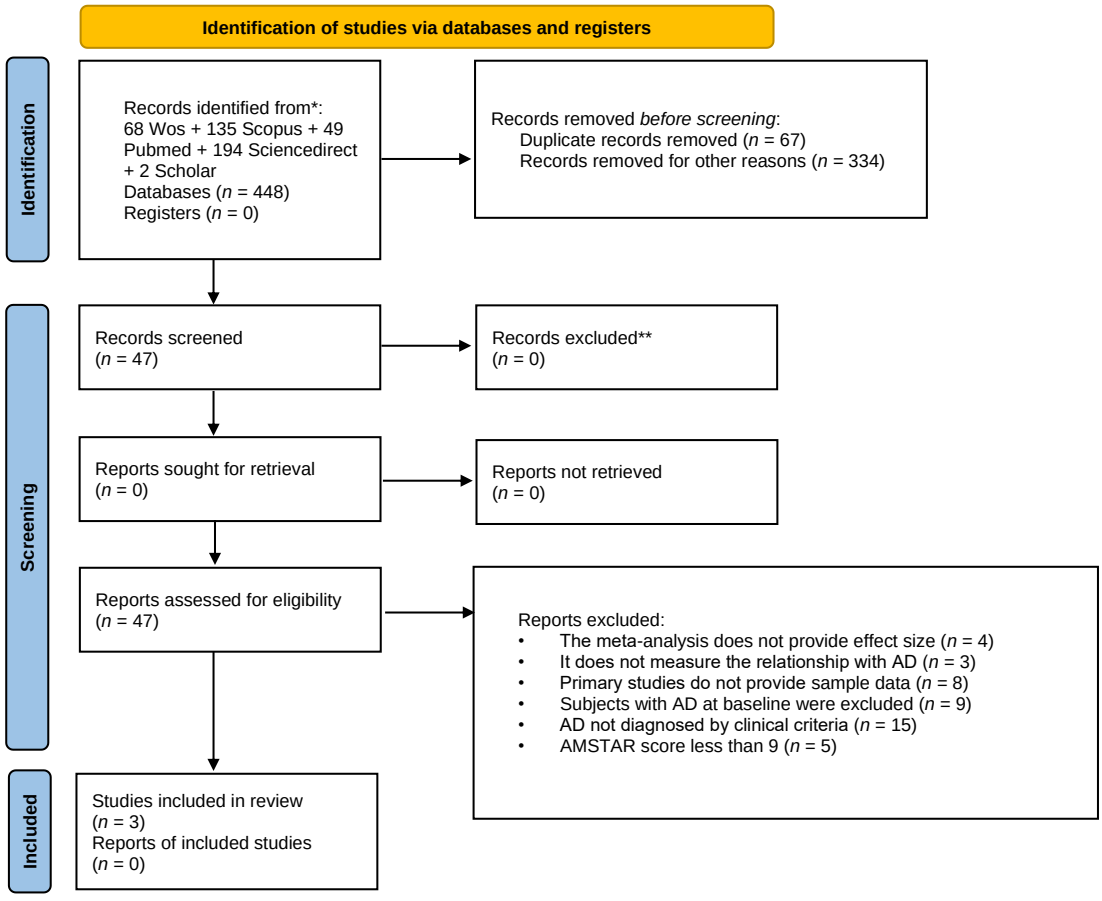

Figura 11. Flow chart depicting the selection of articles for our meta-analysis. Note: AD: alzheimer's disease; n: number of studies

A total of fifty meta-analyses were assessed for eligibility. Of these, some of them were excluded because they: (1) do not report an effect size (n = 4), (2) the primary studies do not measure the relationship between stroke and AD (n = 3), (3) the primary studies do not provide sample data (n = 8), (4) subjects were diagnosed with AD at baseline (n = 9), (5) AD was not diagnosed using a clinical criteria (DSM, ICD, NINCDS) (n = 15), (6) AMSTAR meta-analysis score was lower than 9 (n = 5).

For the estimation of effect sizes of each of the meta-analyses according to the type of stroke, only the studies included in each of the meta-analyses that met the inclusion criteria were considered.

Fourteen effect sizes were extracted from a total of three meta-analyses that included a total of twelve primary studies (Appendix 4: A5). According to the meta-analysis results, k = 8 effect sizes provided information about IS and risk of AD (57,1%); k = 3 about HS (21.4%); k = 3 about MI (21.4%).

For the pooling OR analysis, we analyzed the effect sizes of the primary studies (K = 12).

Tabla 15. Characteristics of the population of the AD and Stroke studies

Study	**Type of stroke**[1]	**Total *N***[2]	***K***[3]	**Country *N***[4]	**% F**[5]	**Age M**[6]	**Results**[7]	**Effect size**[8]			**AMSTAR**[9] **scores**
								Effect size *LogOR*	95 % *CI* LL~UL	*p*	
Pinho et al.(331)	HS	AD *n* = 284 Stroke *N* = 2.201	2	USA (2)	59.06	78	HS > AD	0.57	0.125 ~ 1.008	0.012	9
	MI	AD *n* = 81 Stroke *N* = 139	1	USA (1)	41	79	MI > AD	1.58	1.114 ~ 2.036	0.000	
Cao et al.(332)	IS	AD *n* = 261 Stroke *N* = 680	3	EU (1), USA (2)	50.42	54.8	IS > AD	0.70	0.134 ~ 1.267	0.015	10
	HS	AD n = 51 Stroke *N* = 201	1	EU (1)	21.2	90.7	HS = AD	0.41	-0.693 ~ 1.504	0.469	
	MI	AD *n* = 239 Stroke *N* = 491	3	USA (2)	35	*	MI > AD	0.85	-0.384 ~ 2.074	0.178	
Zhou et al.(30)	IS	AD *n* = 691 Stroke *N* = 13.527	4	EU (2), North America (2)	55.75	73.23	IS = AD	0.89	-0.052 ~ 1.840	0.064	10

Note: [1] Type of stroke. IS: Ischemic Stroke; HS: Hemorrhagic Stroke; MI: Microinfarcts. [2] Total *N*: Total number of cases. AD *n*: Alzheimer cases; Stroke *N*: Stroke cases. [3] *K*: Number of studies. [4] Country *N*: Number of independent studies. EU: European Union; USA: United States of America. [5] % F: Percentage of women. [6] Age M: Mean of age. [7] Sample: AD: Alzheimer cases; IS: Ischemic Stroke; HS: Hemorrhagic Stroke; MI: Microinfarcts. [8] *CI*: 95% Confidence Interval; *RR*: Risk Ratio; *LL*: Lower limit; *UL*: Upper limit. [9] AMSTAR: Assessing the Methodological Quality of Systematic Reviews. https://amstar.ca/Amstar_Checklist.php

Table 15 summarizes key features of the three selected meta-analyses.

The total effect size was *LnOR* = 0.82, *se* = 0.18, 95% *CI* [0.470, 1.169], *OR* = 2.27, 95% *CI* [1.599, 3.218] and heterogeneity was high (*Qb* = 65.98, *df* = 14, *p* = 0.000; I^2 = 78.78). Results did not find differences in effect sizes according to the type of stroke: *Qb* = 3.27, *df* = 2, *p* = 0.195.

I. Ischemic Stroke and AD

Seven primary studies examined IS and AD and reported a significant association between IS and risk of AD (*k* = 8 effect sizes; *N* = 14,207 participants with IS; *n* = 952 with AD and IS). The meta-analyses carried out by Cao et al.(332) (*k* = 4 effect size; *N* = 680 with IS; *n* = 261 with AD and IS) showed a significant association and Zhou et al.(30) (*k* = 4 effect sizes; *N* = 13,527 with IS; *n* = 691 with AD and IS) found no significant association.

The total random effect of the IS and AD value was *LnOR* = 0.79, *se* = 0.29, 95% CI [0.212, 1.362], *Z* = 2.68, *p* = 0.007, I^2 = 84.93. The effect sizes for IS are shown in Table 2.

Tabla 16. Effect sizes related to AD and IS

Study name		**Statics for each study**									
	Sample	***Log OR***	***Se***	***Ve***	***LLIC***	***ULIC***	***Z***	***p***	***OR***	***LLIC***	***ULIC***
Cao et al.(332)											
Brayne et al.(333) (1)	AD *n* = 51 IS *N* = 100	0.64	0.40	0.16	-0.140	1.424	1.61	0.108	1.90	0.869	4.153
Strozyk et al.(334) (1)	AD *n* = 47 IS *N* = 258	0.10	0.51	0.26	-0.895	1.086	0.19	0.850	1.10	0.409	2.962
Strozyk et al.(334) (2)	AD *n* = 84 IS *N* = 143	0.41	0.45	0.20	-0.476	1.287	0.90	0.367	1.50	0.621	3.623
Troncoso et al.(335)	AD *n* = 79 IS *N* = 179	1.39	0.35	0.12	0.706	2.067	3.99	0.000	4.00	2.025	7.899
Zhou et al.(30)											
Qiu et al.(265)	AD *n* = 303 IS *N* = 2.212	-0.20	0.24	0.06	-0.681	0.274	-0.83	0.404	0.82	0.506	1.316
Bermejo-Pareja et al.(336)	AD *n* = 184 *N* IS = 3.864	1.50	0.24	0.05	1.024	1.972	6.20	0.000	4.47	2.784	7.184
Hayden et al.(244)	AD *n* = 121 *N* IS = 3.215	1.86	0.28	0.08	1.303	2.422	6.52	0.000	6.44	3.679	11.266
Lindsay el al.(242)	AD *n* = 83 *N* IS = 4.236	0.43	0.28	0.08	-0.123	0.987	1.53	0.127	1.54	0.884	2.682
Total Random		**0.79**	**0.29**	**0.09**	**0.212**	**1.362**	**2.68**	**0.007**	**2.20**	**1.236**	**3.903**

Note: AD *n*: Alzheimer disease cases; IS *N*: Ischemic Stroke cases. A p-value ≤ 0.05 is statistically significant. Log OR, log odds ratio; Se, estimator bias; Ve, variance statistics; LLIC, Lower Limit confidence interval; ULIC, Upper Llimit confidence interval; Z, standard punctuation; p, statistical significance; OR, odds ratio; LLIC, Lower Limit confidence interval; ULIC, Upper Llimit confidence interval

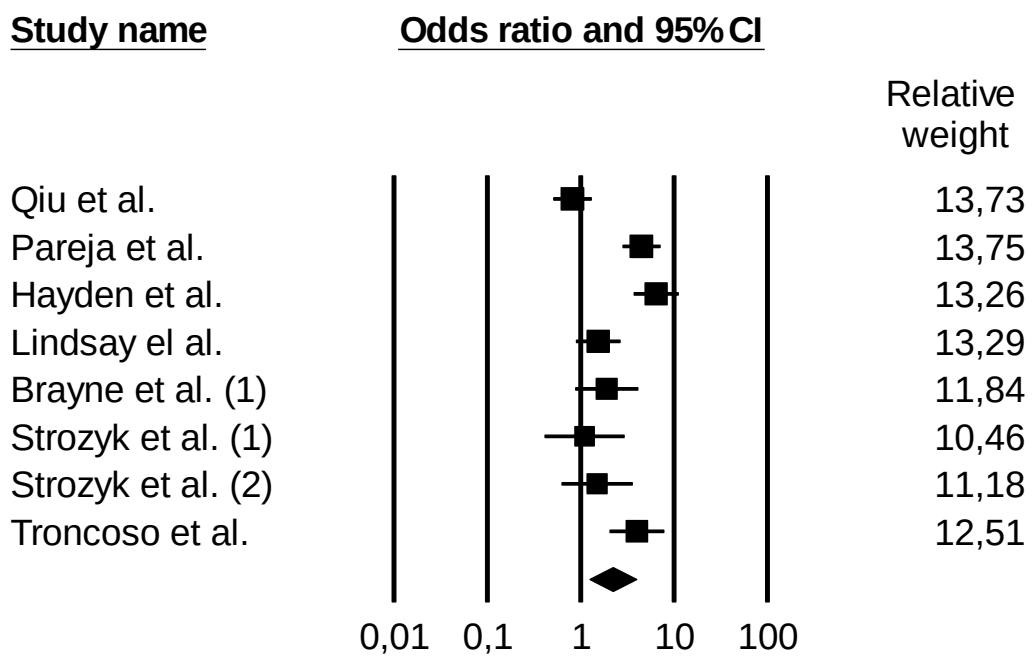

Figura 12. Forest plot of the meta-analysis of incidence rates of AD in patients with IS

II. Hemorrhagic Stroke and AD

Two meta-analyses showed the relationship between HS and AD. Pinho et al.(331) (*k* = 2 effect sizes; *N* = 2,201 participants with HS; *n* = 284 with HS and AD) which showed significant associations between HS and AD; Cao et al.(332) (*k* = 1 effect size; *N* = 201 participants with HS; *n* = 51 with HS and AD) did not found significant associations between HS and AD.

Consistently with Pinho et al.(331), in this meta-analyses (*k* = 3 effect sizes; *N* = 2,402 with HS, *n* = 335 with HS and AD;) a significant association between HS and the risk of AD (*LnOR* = 0.54, *se* = 0.21, 95% *CI* = 0.134–0.954, *Z* = 2.60, *p* = 0.009, I^2 = .000).

Tabla 17. Effect sizes related to AD and HS

Study name	**Statics for each study**									
	Sample	***LnOR***	***Se***	***Ve***	***LLIC***	***ULIC***	***Z***	***p***	***OR***	***LLIC***	***ULIC***
Pinho et al.											
Epstein et al.(337)	AD *n* = 186	0.33	0.61	0.37	-0.873	1.525	0.53	0.594	1.39	0.418	4.597
	HS *N* = 435										
Honig et al.(338)	AD *n* = 98	0.60	0.24	0.06	0.129	1.080	2.49	0.013	1.83	1.138	2.944
	HS *N* = 1.766										
Cao et al.											
Brayne et al.(333)[2]	AD *n* = 51	0.41	0.56	0.31	-0.693	1.504	0.72	0.469	1.50	0.500	4.500
	HS *N* = 201										
Total Random		**0.54**	**0.21**	**0.04**	**0.134**	**0.954**	**2.60**	**0.009**	**1.72**	**1.144**	**2.596**

Note: AD *n*: Alzheimer Disease cases; HS *N*: Hemorrhagic Stroke cases. A *p*-value ≤ 0.05 is statistically significant. Log OR, log odds ratio; Se, estimator bias; Ve, variance statistics; LLIC, Lower Limit confidence interval; ULIC, Upper Llimit confidence interval; Z, standard punctuation; p, statistical significance; OR, odds ratio; LLIC, Lower Limit confidence interval; ULIC, Upper Llimit confidence interval

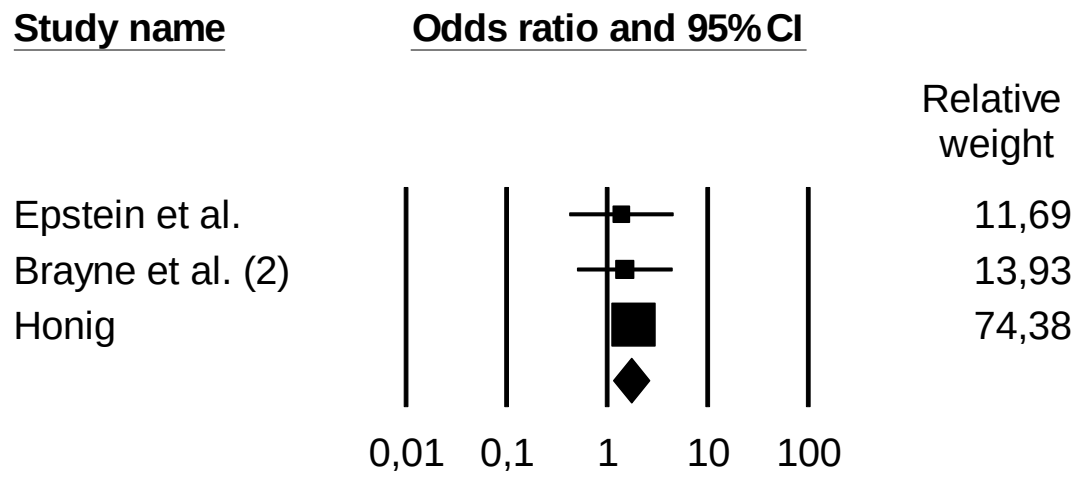

Figura 13. Forest plot of the meta-analysis of risk rates of AD in patients with HS

III. Microinfarcts and AD

Two meta-analyses reported a significant association between MI and risk of AD. In this vein, meta-analyses of studies carried by Pinho et al.(331) (*k* = 1 effect sizes; *N* with MI = 139; *n* = 81 with AD and MI) which showed significant associations between MI and AD and Cao et al.(332) (*k* = 3 effect sizes; *N* with MI = 491; *n* = 239 with AD and MI) did not found significant associations between HS and AD.

As in the study conducted by Pinho, in this meta-analysis found a significant association between MI and AD (*LnOR* = 1.49, se = 0.22 95% *CI* = 1.053, 1.917], $Z = 6.74$, $p = 0.000$, $I^2 = 69.59$).

Tabla 18. Effect sizes related to AD and microinfarcts

Study name		**Statics for each study**									
	Sample	***Log OR***	***Se***	***Ve***	***LLIC***	***ULIC***	***Z***	***p***	***OR***	***LLIC***	***ULIC***
Pinho et al.											
Suter et al.(339)	AD *n* = 81 MI *N* = 139	1.58	0.24	0.06	1.114	2.036	6.69	0.000	4.83	3.045	7.662
Cao et al.											
Arvanitakis et al.(340)	AD *n* = 192 MI *N* = 233	1.39	0.20	0.04	0.989	1.788	6.81	0.000	4.01	2.689	5.979
Sonnen et al.(341)	AD n = 47 MI *N* = 258	0.12	0.52	0.27	-0.892	1.136	0.24	0.813	1.13	0.410	3.115
Total Random		**1.49**	**0.22**	**0.05**	**1.053**	**1.917**	**6.74**	**0.000**	**4.41**	**2.866**	**6.798**

Note: AD *n*: Alzheimer Disease cases; MI *N*: Microinfarcts cases. A *p*-value ≤ 0.05 is statistically significant. Log OR, log odds ratio; Se, estimator bias; Ve, variance statistics; LLIC, Lower Limit confidence interval; ULIC, Upper Llimit confidence interval; Z, standard punctuation; p, statistical significance; OR, odds ratio; LLIC, Lower Limit confidence interval; ULIC, Upper Llimit confidence interval

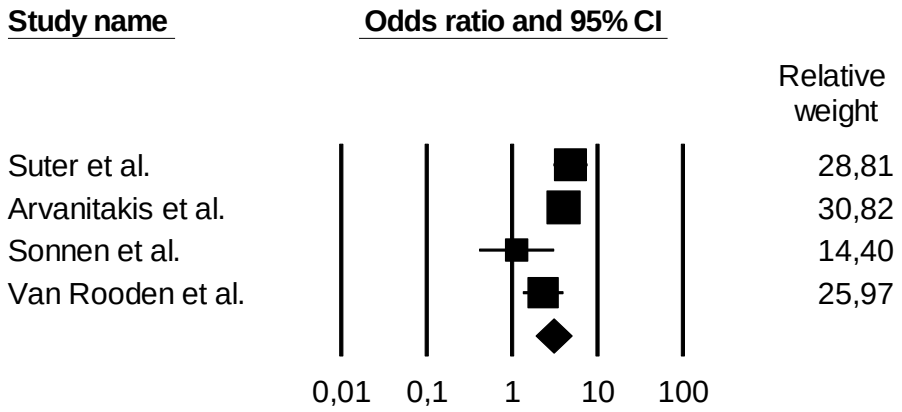

Figura 14. Forest plot of the meta-analysis of risk rates of AD in patients with all types of strokes

IV. Moderating variables analysis

Moderator analyses were performed to explore possible parameters that may explain the differences between the effect sizes. These analyses were performed on categorical variables comparing studies according to sex (0: men and 1: women), age (1. ≤65. 2 >65) and country (1. Europe. 2. North America).

Results showed that there were no differences in the association between Stroke and AD according to sex, age or country. There were also no differences in the relationship between IS, HS and MI with AD according to these variables (See *Qb*). However, regarding sex, in women a significant association is found between IS and AD, but in men it is not significant. Furthermore, as for age, in persons younger than 65 years there is an association between HS and AD, that does not occur in those older than 65 years. Regarding the country, we also highlight that in the North America there is a significant association between all types of stroke and AD, between IS and AD and between HS and AD, while in Europe this association is not significant.

Tabla 19. Effects of sex, age and country in different types of stroke (IS, HS and microinfarcts)

Moderator		**Statics for each study**							
	Variable	*k*	*Log* RR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*	*Qb*
Stroke all types										
Sex	Men	7	0.86	0.22	0.05	0.419	1.295	3.83	0.000	0.02 $p = 0.900$
	Women	8	0.81	0.28	0.08	0.262	1.362	2.90	0.004	
Age	≤65	4	0.85	0.24	0.06	0.377	1.328	3.52	0.000	0.03 $p = 0.853$
	>65	11	0.79	0.25	0.06	0.307	1.270	3.21	0.001	
Country	Europe	5	0.65	0.35	0.13	-0.041	1.342	1.84	0.065	0.43 $p = 0.514$
	North America	10	0.92	0.20	0.32	0.518	1.315	4.51	0.000	
Isquemic Stroke (IS)										
Sex	Men	1	0.64	0.40	0.13	-0.140	1.424	1.61	0.108	0.10 $p = 0.753$
	Women	7	0.80	0.33	0.11	0.160	1.449	2.45	0.014	
Age	≤65	2	0.98	0.53	0.28	-0.070	2.020	2.02	0.067	0.16 $p = 0.692$
	>65	6	0.71	0.39	0.15	-0.041	1.470	1.47	0.064	
Country	Europe	3	0.65	0.58	0.33	-0.483	1.775	1.12	0.262	0.12 $p = 0.725$
	North America	5	0.88	0.35	0.12	0.194	1.574	2.51	0.012	
Hemorrhagic Stroke (HS)										
Sex	Men	3	0.54	0.21	0.04	0.134	0.954	2.60	0.009	0.00

Moderator		**Statics for each study**								
	Women	0	-	-	-	-	-	-	-	$p = 1.000$
Age	≤65	1	0.60	0.24	0.06	0.129	1.080	2.49	0.013	0.24 $p = 0.624$
	>65	2	0.37	0.41	0.17	-0.441	1.179	0.89	0.371	
Country	Europe	1	0.41	0.56	0.31	-0.693	1.504	0.72	0.469	0.07 $p = 0.790$
	North America	2	0.57	0.23	0.05	0.125	1.008	2.51	0.012	
Microinfarcts (MI)										
Sex	Men	3	1.21	0.30	0.09	0.617	1.793	4.02	0.000	0.80 $p = 0.371$
	Women	1	0.84	0.28	0.08	0.288	1.387	2.99	0.003	
Age	≤65	1	0.84	0.28	0.08	0.288	1.387	2.98	0.003	0.80 $p = 0.371$
	>65	3	1.21	0.30	0.09	0.617	1.793	4.01	0.000	
Country	Europe	1	0.84	0.28	0.08	0.288	1.387	2.98	0.003	0.80 $p = 0.371$
	North America	3	1.21	0.30	0.09	0.617	1.793	4.01	0.000	

Note: Log OR, log odds ratio; Se, estimator bias; Ve, variance statistics; LLIC, Lower Limit confidence interval; ULIC, Upper Llimit confidence interval; Z, standard punctuation; p, statistical significance; Qb, heterogeneity between

DISCUSSION

We performed a systematic review of meta-analyses about the relationship between stroke and AD and a meta-analysis of the longitudinal primary studies included in the three selected meta-analyses that met the inclusion criteria. We pooled the prevalence of AD in patients with stroke. Results reported significant association between IS, HS and MI with the risk of AD. Even though results showed heterogeneous effects between studies, this review did not found differences in the association between any type of stroke and AD according to age, sex, or country.

On the one hand, results showed a significant association between IS and risk of AD. The total effect indicated that participants with an incident of IS had more risk to develop AD than healthy people. In this line, several aging-related changes in the brain have been associated with an increase in vulnerability to IS in the elderly (342). An explanation is that IS and AD, despite being distinct disease entities, share numerous pathophysiological mechanisms such as those mediated by inflammation, immune exhaustion, and neurovascular unit compromiso (343) that increase the risk of AD. In this vein, Chi et al. (344) and Vijayan et al. (345) pointed out that IS is the major risk factor for AD.

Furthermore, we found an association between HS and the risk of AD. This finding is consistent with other studies in the literature, where significant associations between HS and AD were demonstrated (346,347). This result could be explained because matter lesions caused by vascular changes in HS may also be associated with AD (348). Moreover, the presence of cerebrovascular injury might cause increased cognitive dysfunction in the presence of a concomitant degenerative process (30).

Finally, we found a significant association between microinfarcts and AD. It is true that MI destruct the integrity of microvascular and microstructural tissue, result in Aβ deposition and tau phosphorylation that form neurofibrillary tangles and associated with the cause of

AD (349). In the same vein, other studies demonstrated an association between MI and AD (350,351). In fact, MI could alter important cognitive networks and thus explain part of the neurological dysfunction that the brain suffers in AD (302).

On the other hand, results showed that there were no differences in the association between Stroke and AD according to the moderator variables: sex, age, and country. Despite finding no moderating effects, we found in women a significant association between IS and AD which is not significant in men. In contrast, the relationship between MI and AD is significant in men and women. Related to sex, other studies have found contradictory results. For instance, Kawas et al. (352) conclude that women who suffered an incident of stroke have a higher tendency to develop AD than men. In fact, some evidence suggests that conditions related to pregnancy and menopause are female-specific risk factors for AD (353). Likewise, literature reveal that premenopausal women may experience less incidence of stroke than men at the same age, however, stroke rates may increase among postmenopausal women (353,354). Therefore, further analysis should be necessary to understand the relationship between sex, stroke, and AD.

Related to age, in participants older than 65 years and younger than 65 years there are an association between all types of strokes and AD, and MI and AD. Some studies have reached contradictory conclusions. For example, Cook et al. (355) concluded that the incidence of stroke among patients with and without AD dementia was higher for the sample aged 50-69 years, but decreases with increasing age. Also, increasing age in people with stroke was associated with a decreased relative risk and an increased absolute risk of AD. Some authors explain that elderly patients may have a poor initial neurological status which can lead to the development of stroke and AD (316). Age has been related to have comorbid conditions such as hypertension, atrial fibrillation, cancer and AD, and were less likely independent before stroke (350). Consistent with our results, Michalski et al. (356) found, in an

experimental study with mice, that after a stroke, myelin basic protein immunoreactivities were strongly affected throughout the ischemic nucleus, the striatum, the ischemic border zone, and the lateral neocortex of the ischemic hemisphere, regardless of age and genetic background. Although, different studies found that the incidence of stroke increases with age (345,349), Kokmen et al. (357) found that the risk of dementia doubled in the stroke cohort during the whole follow-up, even after 25 years, regardless of age. Similar results were found In the Framingham study, 10 years after stroke, after adjustment for age, sex, education, and exposure to individual stroke risk factors (358). However, in this study also found in participants younger than 65 years a significant association between HS and AD, which is not found in people over 65 years of age. Seizures are a risk factor for AD and stroke in younger age people, which it could be an explanation for this fact (355).

Regarding the country, we also highlight that in North America there is a significant association between all types of stroke and AD, between IS and AD, and between HS and AD, while in Europe this association is not significant. Only the relationship between MI and AD is significant in Europe too. In this line, one study concluded that the incidence rate of dementia in Europe has declined by 13% per decade over the past 25 years since lifestyle, education and health interventions (i.e. blood pressure control and antithrombotic medication) which has been established to prevent vascular diseases (359). In fact, in a recent meta-analysis (360), the incidence of stroke found in Europe (204,5 per 100,000 person-year; IC95%: 159,8-249,2) is lower than that reported for the USA, which was 373 (351-396) per 100,000 person-years in the period 1987-2011, with an incidence of 219 per 100,000 person-years in those under 65 years of age and 529 in those over 64. The main discrepancies between the US and European populations are attributed to lifestyle differences, such as the adoption of the Mediterranean diet, which may be associated with a lower risk of stroke (361). In the study by Román et al. (362), the strict Mediterranean diet was attributed to very low prevalence of cardiovascular disease such as stroke. Therefore, the Mediterranean diet

can be considered as a promising tool that can be used for the prevention of AD. Perhaps the US population suffers from more cardiovascular events, hypertension, diabetes, smoking and obesity, which contribute more to stroke risk, by not adopting this lifestyle (360).

The results of our study must be interpreted in the light of some strengths. First, we used a large and well-established primary-care database, whereby a broad range of articles were considered, a total of 12 primary longitudinal studies were analyzed. Second, AMSTAR were applied in order to fulfill criteria for quantitative data synthesis to avoid publication bias. Third, we include the independent selection of studies performed by more than one author. Fourth, the inclusion in this meta-analysis of only longitudinal studies provides more reliable empirical evidence on the force of stroke as a true risk factor for AD. However, our study had a few other limitations. Significant study heterogeneity is probably related to variability in identification of stroke and high variability of the follow-up periods, as well as in other important sociodemographic variables. For example, the estimation of a causal effect for comparison between a disease group and a non-disease group can be subject to bias because of the issue of self-selection associated with a patient's specific prognostic factors. In large observational studies, cases and controls often display significant differences in several characteristics.

In the line of future research, several questions remain unresolved. On the one hand, the influence of changes in the white matter and the associated Alzheimer pathology, and on the other hand, the influence of the pre-existing cognitive state in stroke and AD. In addition, the possibility of having AD without stroke should be investigated. Another line of research could be the clinical relevance of silent infarcts for all types of dementia. In summary, future research should focus on the incidence and prevalence of Alzheimer's

disease after stroke, predisposing etiologies of stroke, pre-stroke impairment, and imaging factors that determine the state of the brain after suffering a stroke.

CONCLUSION

Our study describes incidence rates of AD in patients with episodes of stroke (IS, HS and MI), and suggests that the risk of AD may be higher in patients that suffer stroke when compared to matched controls without incidence of stroke. Moreover, moderator analysis supports the robustness of our results. The association between the incidence of stroke and AD was consistent through sexes, age groups and countries. Because stroke occurs more frequently than developing AD and stroke is more common than dementia, some AD disease could be prevented by preventing stroke. Our findings are important to plan health care resources for patients with AD. Stroke is a modifiable risk factor and preventive measures could be established to prevent or delay AD. Promoting changes in lifestyle, for example, prevent an unhealthy diet, cardiovascular diseases, hypertension, smoking, diabetes, obesity, metabolic syndrome, depression, and traumatic brain injury could reduce the risk of stroke and AD. Moreover, this study allows clinicians to consider stroke occurrence when predicting prognosis in patients with AD.

CONCLUSIONS SECTION 1

"Gracias a la memoria se da en los hombres lo que se llama experiencia.".

(Aristóteles, 384 AC – 322 AC, Filósofo griego)

CONCLUSIONS SECTION 1

The first section of this research has aimed to determine and analyze some of the risk factors associated with AD. Research on AD is a priority for several reasons, including the fact that the prevalence of this disease is very high in our society. Moreover, it is a growing public health problem which involves functional and cognitive decline in the elderly and generates dependence (363). In addition, there is agreement that the non-health costs associated with AD (informal care costs and indirect costs) are greater than those are greater than health costs associated with AD (364).

We start from the systematic review shown in the first chapter, which elucidates the most important modifiable risk factors in the study of AD, from which four of the factors were selected for further analysis. These factors increase the risk of developing AD. Among these factors are stroke, hypertension, and cholesterol (365,366). There are several strong arguments for studying these variables in-depth. On the one hand, the association of cardiovascular risk factors may be due to shared risk factors between vascular diseases – such as stroke, hypertension, or cholesterol – and AD, but there could also be a direct causal association, since heart disease causes hypoperfusion and micro emboli, which are implicated in the etiology of AD (367). The coexistence of anatomopathological lesions typical of AD and vascular lesions has been demonstrated by autopsy (368). This influence could be due to direct effects of beta-amyloid protein accumulation in the brain. In addition, elevated brain insulin values are known to decrease beta-amyloid protein metabolization (369). On the other hand, depression may confer an increased risk of developing AD in the future. Depression is a disease whose incidence is on the rise (18.4% increase between 2005 and 2015) (370), and it could affect AD through the lifestyle adopted as previous studies have found that this mental disorder is negatively associated with a healthy lifestyle (371,372). A better understanding of the relationship between depression and AD may have important

implications for public health (373). This section will discuss the results of the meta-analyses conducted in Chapters 2, 3, 4, and 5 where the relationship of AD with cholesterol, depression, blood pressure, and stroke has been examined.

CHOLESTEROL AND AD

The first meta-analysis examined the relationship between cholesterol, cholesterol type (high levels of low-density lipoprotein (LDL-C), low levels of high-density lipoprotein (HDL-C), triglycerides (TG), and total cholesterol (TC)) and the risk of developing AD. The literature review allowed us to analyze 5 meta-analyses, from which 100 primary cross-sectional and longitudinal studies including 2,289,511 participants were selected to analyze 12 effect sizes.

Confirming the results from existing literature (8,32,43,83), the overall results revealed that cholesterol level is a risk factor for AD (374). Cholesterol levels in the brain are tightly regulated by physiological brain function, but growing evidence indicates that excess cholesterol accumulates in the brain, where it can cause pathological changes associated with AD(374).

After the analysis of different types of cholesterol, it was concluded that an elevated LDL cholesterol level was an independent risk factor for the development of AD. The pooled effect size showed a significantly increased risk of developing AD for individuals with higher LDL-C levels, which is also in agreement with the literature, where LDL concentration in mid-life is shown to increase the risk of developing AD later in life (105).

However, the results showed no difference in serum HDL levels between healthy and AD subjects. This result remains controversial, and no conclusive evidence was found. Several studies indicated that variations in serum HDL lipid levels are not associated with AD (8,32,43,63); but, in other studies, lower HDL levels have been associated with a higher risk of developing AD (106,109). In addition, another study suggests that elevated HDL levels

are associated with a lower risk of dementia, and that HDL may protect people against cerebrovascular dysfunction in AD (114).

Triglycerides are a type of lipoprotein that accumulate in the arteries and can produce adverse side effects in the human body (375). Triglyceride (TG) levels also did not show a positive association with the development of AD. In retrospective studies, the use of drugs to reduce cholesterol levels could reduce the likelihood of finding an association between TG and AD (117,118).

As for TC (total cholesterol), the results found no significant effect of TC levels on AD. Several studies claim that high cholesterol levels in middle age represent a risk factor for AD, but that there are no detectable differences in cholesterol levels at older ages (31,63,114). Therefore, the non-significant effects of TC on AD in prospective studies (30 years of follow-up) could be explained by variation in TC levels and disease progression.

In summary, this research indicated that there is an association between cholesterol level and AD. Therefore, LDL-C, HDL-C, TG, and TC were analyzed separately as risk factors for AD. This study highlighted the need to analyze other factors related to AD. Indeed, physical activity and the use of drugs could reduce the effects of cholesterol on AD. Overall, this meta-meta-analysis represents a step towards empirical evidence-based knowledge of AD which could have a huge beneficial impact on the incidence and prevalence of the disease.

DEPRESSION AND AD

In the second meta-analysis performed, the main contribution was based on producing precise estimates of the risk of developing AD associated with different criteria of depression, either clinically significant or based on symptomatic scales. Six meta-analyses were included, from which 28 longitudinal studies analyzing 28 effect sizes were selected. The total sample consisted of 101,881 participants. A total of 17 studies were based on

symptomatic rating scales, and 11 studies were based on clinical criteria for assessing depression: CES-D, DSM-III/III-R/IV/V, GMS-AGECAT, GDS, and HAM-D.

The random effect of the relationship between depression and AD was significant. Eleven studies found a more than 3-fold increased risk of developing AD for participants diagnosed with clinically significant depression. Also, based on the results of the 17 studies based on the symptomatic depression rating scales, the risk of developing AD was almost twofold. We found that studies using clinically meaningful criteria for the diagnosis of depression had more consistent and significant results than those using symptomatic scales.

On the other hand, this meta-analysis focused on analyzing the predictive effect of the different cut-off points of the symptomatic CES-D scale, as it was the most widely used in the selected studies. A slightly significant predictive effect was found in studies using CES-D cut-points ≥10 and ≥16, but the predictive risk of developing AD was higher for a study using a more restrictive cut-point (≥20). These results were consistent with those of Cherbuin et al. (35) who found that studies using a previously validated cutoff point against clinical criteria (≥20) demonstrated higher risk estimates than those using a more permissive cutoff point (≥16).

Although we cannot yet assert an etiologic basis for the association between AD and depression, our study provides consistent data pointing to an increased risk of developing AD for clinically significant depression. These findings underscore the importance of using more stringent and objective measures of depression in future studies. Depression should be assessed by professionals with standardized and validated measures, and preventive strategies targeting at-risk individuals should be designed. Further studies should evaluate the possibility that treatment of clinically significant depression decreases the risk of developing AD.

BLOOD PRESURE AND AD

In the third meta-analysis, the association between elevated blood pressure (BP) and the risk of developing AD was studied. Information was established on the types of hypertension (Diastolic Blood Pressure (DBP), Systolic Blood Pressure (SBP), and Combined Blood Pressure (CBP)) and AD. Twenty-five meta-analyses were selected in this study, from which fifty-two primary studies, both cross-sectional and longitudinal, and seventy-five effect sizes were extracted. The total sample size was 1,485,392 participants. Overall, the results indicate that hypertension was associated with an increased risk of developing AD.

The results showed that participants with elevated SBP were at an increased risk of developing AD, and supported the findings of previous studies suggesting that there was consistent evidence of an effect of systolic hypertension on AD.

However, this meta-analysis did not find a significant association between elevated DBP and the risk of developing AD. According to previous studies, these results could be explained by confounding variables due to associations between BP and chronic disease or other unknown modifiable risk factors (277–279).

In relation to combined arterial hypertension (CAP) (i.e. high SBP and DBP), only one meta-analysis (278) compared the incidence of AE between subjects with and without hypertension. These studies found that elevated BP was not associated with an increased risk of developing AD. This result is contradictory to those found in other studies such as Guan et al. (15).

To explore the influence of other research parameters on the relationship between elevated SBP and DBP with AD, different moderators were analyzed: type of measurement, sex, age, study design, and world region. This study found no differences in the risk of developing AD according to the type of measurement for SBP (>140 and >160) and DBP (>85, >90).

Total scores revealed significant differences between men and women only in the relationship of elevated DBP and AD. So the data suggested that women with elevated DBP (>90 mmHg) had an increased risk of developing AD compared to men (an increased AD risk level of 86%).

Age at onset (≤65 years early onset and ≥ 65 years late onset) did not moderate the relationship between elevated SBP and AD. Total scores showed that age was associated with an increased risk of developing AD at both early (10%) and late (7%) onset. However, this study found that elevated SBP > 160mmHg significantly increased the risk of dementia in participants aged <=65 years (<=65), but not in those >= 65.

These results found no differences in the effect size of the association between elevated SBP and DBP and AD risk according to the type of design (cross-sectional and longitudinal). The results found an association between BP and risk of developing AD in both types of studies. Along these lines, the relationship between elevated SBP and AD is significant in longitudinal studies and with SBP > 160mmHg (23% increase), whereas elevated DBP (>85, > 90mmHg) is not related to an increased risk of developing AD.

Finally, the region of the world is the only variable that moderated the relationship between hypertension and AD. An increased risk of developing AD was observed in persons with hypertension from Asian and North American countries, but not in those from European countries. Looking at the BP measurement, people from Asian countries with SBP>140mmHg were more likely to have AD (an increase of 34%) compared to North American and European countries. A significant risk of AS related to SBP>160mmHg was also shown in Europe and Asia and was not found in North America.

In summary, this study found that BP, and particularly SBP, is associated with an 11% increased risk of AE. Neither SBP and DBP effect sizes, gender, age, nor study design moderated the relationship between BP and AD. The only significant moderator was world

region, with Asian and North American countries showing stronger effect sizes between BP and AD risk than European countries. Future work should use other uncontrolled factors (e.g., cardiovascular disease, diabetes, and stroke) to explain the relationship between elevated BP and AD. Some studies have linked hypertension to brain atrophy, white matter lesions, and neurofibrillary tangles (376). Along these lines, explanations linking cardiovascular disease and AD include a shared etiology, as atherosclerosis plays an important role in both cardiovascular pathology and AD (376,377). Thus, there is evidence that pathologies of vascular origin play an important role in the etiology of AD. Although for some of these factors the mechanisms that are linked to AD are clear, for others the association with AD is more complex and needs further investigation to be fully deciphered.

STROKE AND AD

Finally, a systematic review of the available literature and a meta-meta-analysis of the longitudinal primary studies contained in the selected meta-analyses that met the inclusion criteria for analyzing the relationship between stroke and AD were performed. Three meta-analyses were included in this study, from which a total of 13 primary studies (16,547 participants) were selected and 14 effect sizes were extracted. A significant association was found between stroke and an increased risk of developing AD. Although the results showed heterogeneous effects across studies, the review found no difference in the association between any type of stroke and AD.

First, the results showed a significant association between IS (Ischemic Stroke) and risk developing of AD. The total effect indicated that participants who suffered from an IS were at higher risk of developing AD than healthy individuals. Along these lines, several aging-related changes in the brain have been associated with an increased vulnerability to IS in the elderly (342).

In addition, an association was also found between HS (Hemorrhagic Stroke) and the risk of developing AD. This finding is consistent with other studies in the literature, in which significant associations between HS and AD were demonstrated (346,347).

Finally, a significant association was found between MI (microinfarcts) and AD. Previous studies also demonstrated an association between MI and AD. (350,351). In fact, MI may alter important cognitive networks and thus explain part of the neurological dysfunction suffered by the brain in AD (302).

On the other hand, the results showed that there were no differences in the association between stroke and AS according to the moderating variables (sex, age, and world region). Although no moderating effects were found, a significant association was found between IS and AD in women which was not significant in men. In contrast, the relationship between MI and AD is significant in both sexes. Kawas et al. (352) concluded that women who have suffered a stroke have a greater tendency to develop AD than men.

Age was not a factor when studying the association between all types of stroke and AD, and between MI and AD. Michalski et al. (356), in an experimental study, examined the neurobiological changes that occur after stroke, independent of age and genetic load. This helps to understand why a stroke may be associated with an increased risk of developing AD at any age. However, in participants younger than 65 years, we found a significant association between HS and AD that was not found in people older than 65 years.

Although the world region does not moderate the relationship between stroke and AD, in North America there is a significant association between all types of strokes and AD, between IS and AD, and between HS and AD, whereas in Europe this association is not significant. However, the relationship between MI and AD is significant in both regions of the world. One of the main discrepancies between Europe and North America is related to

lifestyle, such as the adoption of the Mediterranean diet, which may be associated with a lower risk of stroke (361).

This chapter describes the incidence rates of AD in patients with stroke episodes (IS, HS, and MI), and concludes that the risk of developing AD may be higher in stroke patients compared with matched controls with no incidence of stroke. Furthermore, moderation analysis supports the robustness of our results. The association between stroke incidence and AD was consistent across sexes, age groups, and regions of the world. Given that stroke occurs more frequently than the development of AD, and that stroke is more common than dementia, some AD could be prevented by preventing stroke. These findings are important for planning health care resources for patients with AD. Stroke is a modifiable risk factor, and preventive measures could be established to avoid or delay AD. Promoting lifestyle changes, e.g., preventing an unhealthy diet, cardiovascular disease, hypertension, smoking, diabetes, obesity, metabolic syndrome, depression, and traumatic brain injury could reduce the risk of stroke and AD. In addition, this study allows clinicians to take stroke occurrence into account when predicting prognosis in patients with AD. Pooling all the effects extracted from the meta-analyses performed with the different risk factors, the largest effect sizes are for: Depression (OR = 2.46) and Stroke (OR = 2.27). The largest effect size is found in the relationship between MI and AD (OR = 4.41). Another of the highest effect sizes is found between the association between LDL cholesterol type and AD (OR = 2.55). Along the same lines, IS is also a variable that is strongly associated with AD, with an effect size of OR = 2.12.

SUMMARY OF POOLED EFFECT SIZES

Tabla 20. Summary of pooled effect sizes

Variable	Type of variable	*OR/RR*	*LLIC*	*ULIC*	*Z*	*p*
Cholesterol (OR)		**1,29**	**1.04**	**1.60**	**2.28**	**0.023**
	LDL	2,55	1.25	5.22	2.57	0.010
	HDL	0,87	0.64	1.18	-0.89	0.372
	TC	1,44	0.91	2.28	1.55	0.121
	TG	1.22	0.96	1.56	1.64	0.102
Depression (OR)		**2.46**	**1.81**	**3.35**	**5.72**	**0.001**
	Clinic	1.80	1.16	2.78	2.62	0.009
	Sintomatic	1.68	1.24	2.27	3.36	0.001
Blood pressure (RR)		**1.08**	**1.032**	**1.133**	**3.27**	**0.001**
	SBP	1.09	1.013	1.181	2.28	0.022
	DBP	1.16	0.956	1.402	1.50	0.133
	CBP	1.02	0.836	1.249	0.21	0.835
Stroke (OR)		**2.27**	**1.599**	**3.218**	**4.86**	**0.000**
	Ischemic	2.12	1.304	3.447	3.03	0.002
	Hemorrhagic	1.72	1.144	2.596	2.60	0.009
	Microinfarcts	4.41	2.866	6.798	6.74	0.000

Note: OR, odds ratio; RR, risk ratio; LLIC, Lower Limit confidence interval; ULIC, Upper Limit confidence interval; Z, standard punctuation; p, statistical significance

FUTURE LINES

Efforts to understand Alzheimer's disease and related disorders from a more holistic point of view are increasing. Several vascular, lifestyle, psychological and genetic risk factors have been recognized as influencing the development of AD and may act independently and potentiate each other in the progression of AD. AD is increasingly being recognized as a

complex multifactorial disease attributable to several interrelated and interacting risk factors (378).

Research on AD has undergone a paradigm shift from viewing it as a disease of old age to adopting a life course perspective. The common factor in this research is the multidomain approach that aims to simultaneously address several modifiable risk factors (vascular and lifestyle-related risks) that are present in young adults. Hence the importance of primary prevention where the risk factors that cause AD for multiple reasons must be determined.

1- AD occupies the top rankings for mortality in most countries. It is arguably the most costly disease in the world, with an annual cost of $200 billion in the United States alone (88). Thus, economists predict that preventing, or at least delaying, the onset of the disease by five years would cut costs by half.
2- Without intervention, the number of individuals with AD will skyrocket in the coming decades. By 2050, the number of people with AD dementia in the United States will be 13.5 million, and the costs will increase fivefold (88). The care provided to people with AD has drastically affected our healthcare system, causing caregiver overload, loss of productivity, and out-of-control costs.

Therefore, the study of potential risk factors for AD, as addressed in this section of the thesis, and the implementation of early interventions, could lay the groundwork for long-term solutions to address this growing chronic problem.

In relation to the study of risk factors, vascular factors such as cholesterol, blood pressure, and stroke have been analyzed in some chapters. In this regard, it would be interesting to analyze other cardiovascular risk factors such as diabetes mellitus, existing cardiovascular disease, smoking, and drinking. In recent years, there is increasing evidence that AD and cardiovascular disease may be closely related and the study of these variables could clarify this relationship.

It might also be useful to analyze other variables, such as age, separately. Even though the age variable is not significative as a moderator in some chapters of this section, an analysis of age as an independent variable could be interesting. The vast majority of AD cases have a late onset (usually after the age of 65); the disease is rare among younger individuals(379). The incidence of AD is known to increase with age, and age is the most important risk factor for the development of AD. The number of people with AD approximately doubles every 5 years after age 65. Approximately one third of all people over the age of 85 may have AD.

Finally, it seems feasible to analyze secondary factors such as depression, anxiety, schizophrenia, bipolar disorder, and other risk factors that do not directly affect AD, but whose development would alter otherwise healthy lifestyles and have an impact on the development of AD. In this sense, these pathologies would promote less healthy lifestyles and would have an impact on cardiovascular and cerebral health which are direct risk factors for AD. In Chapter 3 of this section corroborated the association between being diagnosed with depression and developing AD. Within this line of research, other pathologies, such as anxiety or schizophrenia, could be studied.

SECCIÓN 2

UN ESTUDIO DE OPTIMIZACIÓN HEURÍSTICA, MINERÍA DE DATOS Y ENFOQUE MULTI-OBJETIVO

CAPÍTULO 6

"No hay olvido que valga, tú guarda los sentimientos que yo guardo los recuerdos.".

(@EF_Roberto, 2018)

Pacheco JA, Saiz-Vazquez O, Casado S, Ubillos-Landa S. A multistart tabu search–based method for feature selection in medical applications Neural Comput Appl. 2023 (in review)

CAPÍTULO 6: DESARROLLO DE UN SISTEMA GENERADOR DE MODELOS PARA DIAGNOSIS MÉDICAS

ABSTRACT

When designing classification models we often find attributes that turn out to be irrelevant or noisy. We can also find attributes with negative interaction with other attributes. All this can impair the performance of the models. Attribute selection is a task that searches for a small subset of relevant attributes from the original set that result in the most efficient models possible. In addition to improving efficiency, variable selection brings other important advantages, such as easier to obtain the necessary data, clearer and better interpretable models, etc. In the case of applications in medicine, the selection of attributes can help to distinguish which characteristics, habits, factors, etc., have the greatest impact on the appearance of diseases. However, feature selection is a complex task due to the large number of possible solutions. In recent years, methods based on different metaheuristic strategies, mainly evolutionary algorithms, have been proposed. In this paper, a simple method based on tabu search and muti-boot techniques is proposed. The proposed method has been analyzed and compared on different known medical databases. These computational tests show the better performance of this method against other recent methods considering different metrics and classifiers. Statistical tests are provided to reinforce these conclusions.

Keywords: classification, feature selection, medical diagnosis, tabu search

INTRODUCCIÓN

El diagnóstico consiste en un proceso en el que se identifica una enfermedad, afección o lesión por sus signos y síntomas. Para ayudar a hacer un diagnóstico, se pueden utilizar los antecedentes de salud o realizar un examen físico y pruebas, como análisis de sangre, pruebas con imágenes y biopsias. La diagnosis es un procedimiento en constante evolución para la mayoría de patologías, que se centran en realizarla lo más rápido y con la mayor predicción posible(380).

El diagnóstico precoz en medicina es vital para algunas patologías. Por una parte, gracias a la detección temprana, se logra mejorar la supervivencia en patologías como el cáncer de páncreas(381), por otra parte, el diagnóstico precoz es crucial para la mejora en el pronóstico de la enfermedad como en tumores o melanomas(382). En otros casos como la diabetes, el diagnóstico precoz se convierte en algo imprescindible para paliar las complicaciones secundarias de la enfermedad: lesiones arteriales, colesterol, hipertensión, obesidad o infarto de miocardio (383). La diagnosis en la EA, es de suma importancia también, ya que ha ayudado a su diagnóstico en las primeras etapas y ha facilitado el diagnóstico diferencial entre la EA y otros trastornos neurodegenerativos con demencia(384).

La minería de datos (385,386) es una técnica que ha permitido el análisis de grandes volúmenes de información dando como resultado patrones o reglas que ayudan a entender el comportamiento de un sistema(387). En medicina se ha convertido en un campo emergente de gran importancia que proporciona un pronóstico y una comprensión más profunda de la clasificación de las enfermedades (388). Con distintos modelos como la Regresión Logística (RL)(389), Análisis Discriminante (ADL) (390), Support Vector Machine (SVM) (391), Redes Neuronales (RN) (392), Árboles de Clasificación (393), vecino más cercano (394), clasificadores bayesianos (395)… se logra realizar un diagnóstico temprano. En la mayoría de los usuarios, para el diagnóstico de EA, es necesario recurrir a

detallados exámenes físicos y pruebas cognitivas que miden distintas funciones cognoscitivas y las actividades cotidianas relacionadas con el funcionamiento del cerebro (5). Es por ello por lo que un diagnóstico precoz y preciso de la EA sería crucial para pacientes y sus familias. Les ayudaría a planificar el futuro y buscar opciones de tratamiento, mientras el paciente puede seguir participando en la toma de decisiones(396).

Uno de los problemas que surgen en la actualidad en referencia a "machine learning" o "aprendizaje automático", es identificar un conjunto representativo de características a partir de las cuales construir un modelo de clasificación para una tarea en particular (397). La selección de variables, por tanto, se ha convertido en una necesidad urgente para buscar el subconjunto óptimo de características (398). Esta selección es una tarea importante para reducir la dimensionalidad de los datos y aumentar el rendimiento de un algoritmo de clasificación (399,400). Se han explorado muchos enfoques de búsqueda para descubrir un subconjunto significativo de las características que produzca una mayor precisión (401), ya que el objetivo es mantener la cantidad de características lo más pequeña posible para reducir el costo computacional de entrenar un clasificador, así como la complejidad del algoritmo (402,403).

En la práctica, el conjunto óptimo de características generalmente se desconoce y es común por tener características irrelevantes o redundantes al comienzo del proceso de reconocimiento de patrones (402). Por lo tanto, en los distintos modelos de clasificación, surgen además de fortalezas, también debilidades que conduce a un campo inconexo y fragmentado donde en ocasiones es difícil mejorar el rendimiento de modelos y algoritmos y tener éxito en la clasificación (399). Es por ello que cobra importancia la selección de funciones donde se incluya la creación de modelos más simples y comprensibles, la mejora del rendimiento del propio modelo y, además, la preparación de datos limpios y

comprensibles (400,404). Ser capaz de reducir la complejidad del modelo puede ayudar a mejorar la precisión del rendimiento del modelo de clasificación (405).

METODOLOGÍA

I. Métodos de selección de variables

Los métodos de selección de variables se pueden clasificar en tres tipos: filter, wrapper y embedded (400). Los métodos filter seleccionan un cierto número de variables basándose en criterios como la correlación, la similitud, la ganancia de información, etc., sin que intervenga ningún clasificador (400,404). Algunos ejemplos de métodos filter son los siguientes algoritmos: Correlation Feature Selection (CFS) o algoritmo de correlación (385), Mutual Information (MI) (402), ReliefF algorithm (386), Chi-square algorithm (406), Fisher Score algorithm (407) y Fast Correlation-Based Filter (FCBF) (408).

Los métodos wrapper intentan obtener todas las combinaciones de variables para evaluar la utilidad de cada uno de los subconjuntos mediante la eficacia predictiva de un clasificador concreto, teniendo como objetivo encontrar el mejor subconjunto de variables. Normalmente se obtienen mejores resultados con los métodos wrappers que con los métodos filters dado que estos últimos carecen de la evaluación del rendimiento de las variables seleccionadas con un clasificador determinado (409), aunque los métodos wrapper requieren de mayores tiempos de computación que los métodos filter.

Debido a la robustez de las técnicas metaheurísticas en diversas aplicaciones complejas, algunas de ellas se han utilizado para crear métodos wrapper de selección de variables: Algoritmos Genéticos (410,411), Grey Wolf Optimizer (GWO) (410,412), Flower Pollination Algorithm (413,414), Bat Algorithm (415,416), Ant Colony Optimization (403,417), Whale Optimization Algorithm (418,419), Particle Swarm Optimization

(409,420), Harmony Search Algorithm (401,421), Harris Hawks Optimization Algorithm (398,405) y Búsqueda Tabú (422,423).

Finalmente, los métodos embedded integran la selección de variables y el aprendizaje del clasificador en un único proceso. Estos métodos se han usado en trabajos como Queen and Emrich 2021. (424), Liu et al. 2019. (425) y Pacheco et al. 2007. (426).

II. Literatura sobre selección de variables en medicina

Se han utilizado diferentes enfoques dentro de modelos lineales que apoyan el modelo y que además predicen con alta precisión usando características de distintas variables(427); es el caso por ejemplo del estudio realizado por Jothi et al. (428), en el que se extraen diferentes categorías de características de las imágenes de resonancia magnética segmentadas (intensidad y textura) para seleccionar las características imperativas del tumor cerebral. En este mismo sentido y a partir de imágenes de resonancia magnética, Dimitriadis et al.(429). cuantificaron la precisión de predicción de múltiples características morfológicas para diagnosticar la EA y definir biomarcadores únicos y multimodales para la EA. En el estudio realizado por Liu et al. (430), el método FIG brindó el mejor rendimiento de reconocimiento no solo que el conjunto completo de características originales sino también cualquier tipo de características individuales para el reconocimiento de enfermedades pulmonares. Del mismo modo, en el estudio realizado por Chong et al. (431) se construyó un clasificador que le permitió detectar en imágenes de tomografía computarizada, enfermedad pulmonar intersticial fibrótica utilizando características de textura 3D. Shi et al. (432) utiliza un método de segmentación basado en el aprendizaje a través de la selección de características conjuntas y, que incorpora la especificación manual simple del médico, para ayudar a la segmentación precisa, especialmente para hombres con problemas de próstata irregular grande. En esta misma patología, Guinin et al. (433). proporcionaron una herramienta de segmentación automática para la radioterapia prostática y Sharan et al. (434) propusieron un nuevo método

de selección de características que clasificara y diagnosticara imágenes histopatológicas de próstata. También se han realizado estudios para otros tipos de cáncer como Jain et al. (435), que propone un modelo híbrido basado en la optimización mejorada para el diagnóstico y la clasificación del cáncer. Wang et al. (436) utilizan una estrategia de selección de características ponderada e integra algoritmos basados en bacterias para reducir la dimensión de la característica en la clasificación en distintos tipos de cáncer de expresión génica. Kang et al. (437) utilizan un nuevo método (RL-SVM) para la clasificación de tumores en conjuntos de datos de tumores de dos clases y de varias clases. También se han usado algoritmos de selección de características mediante el clasificador Adaboost para detectar Glaucoma (438).

III. Formulación de problema de selección de variables

Para formular el problema que se trata en este trabajo (selección de variables para clasificación) se define conjunto de entrenamiento a los datos con los que vamos a generar los modelos. Así mismo se denota por n al número de individuos de dicho conjunto y a m el número de variables. Al conjunto de variables lo denotamos por V y por v_j a la variable j-ésima, es decir

$$V = \{v_1, v_2, v, \dots, v_j, \dots, v_m\}.$$

Al conjunto de entrenamiento lo denotamos por X. A un individuo genérico (sea del conjunto de entrenamiento o no) lo denotamos por $\boldsymbol{x}$. A cada individuo $\boldsymbol{x}$ se le identifica con el vector de los valores de sus variables, es decir

$$\boldsymbol{x} = (x_1, x_2, x_3, \dots, x_j, \dots, x_m)'$$

A los individuos del conjunto de entrenamiento los denotamos por $\boldsymbol{x_i}$, $i = 1, \dots, n$. De esta forma

$$\boldsymbol{x_i} = (x_{i1}, x_{i2}, x_{i3}, \dots, x_{ij}, \dots, x_{im})'$$

por tanto x_{ij} es el valor de la variable v_j, $j = 1, \dots, m$.

Vamos a considerar problemas de clasificación binaria, es decir, con 2 clases, ya que lo vamos a aplicar a la diagnosis de enfermedades, y por tanto hay dos clases: tener la enfermedad o no. La clase de cada individuo $\boldsymbol{x}$ se representa por una variable binaria $\boldsymbol{y}$. En el caso de un individuo $\boldsymbol{x_i}$ del conjunto de entrenamiento la representamos por $\boldsymbol{y_i}$. Denotamos por G_k, al conjunto de individuos de la clase k, $k = 0,1$. Por tanto, si $y_i = k$ entonces $\boldsymbol{x_i} \in G_k$, (k = 0,1).

Sea p el número de variables que queremos seleccionar ($p < m$), el problema consiste en encontrar el subconjunto $S \subset V$, verificando $|S| = p$, con mayor capacidad clasificatoria. Esta capacidad clasificatoria para un subconjunto $S \subset V$ (que denotamos como $f(S)$) se define como la ratio de casos de X bien clasificados usando las variables de S con el clasificador obtenido con el modelo considerado. En nuestro caso, como se ha comentado antes se consideran 3 modelos lineales: LDA, LRA Y SVM.

IV. Método de solución para el problema de selección de variables

El método de solución es un procedimiento (que denominamos *MultiStartTabu*) que usan combinadas la estrategia multi-arranque y la búsqueda tabú. En cada iteración se ejecutan dos procedimientos: un procedimiento constructivo (que denominamos *Constructive*) que genera una solución inicial y un procedimiento que mejora la solución generada por el constructivo. Este procedimiento de mejora está basado en la estrategia búsqueda tabú (y por tanto lo denominamos *TabuSearch*). El método finaliza cuando transcurren una serie de iteraciones sin mejorar la mejor solución encontrada. El pseudocódigo 1 muestra el método M*ultiStart*.

Method $MultiStartTabu$

$iter = 0, iterbest = 0, f^{best} = 0$

Repeat

1. $iter = iter + 1$
2. Execute $Constructive(\alpha, S)$
3. Execute $TabuSearch(tenure, maxiter, S, S^*)$
4. **if** $(f(S^*) > f^{best})$ **then** $S^{best} = S^*$, $f^{best} = f(S^*)$ and $iterbest = iter$

until $(iter - iterbest \geq maxiterMS)$

Pseudocode 1. $MultiStart$ Method

Como se puede observar, $iter$ es una variable auxiliar que indica el número de la iteración actual; $iterbest$ indica la iteración donde se ha encontrado la mejor solución; S^{best} y f^{best} son respectivamente la mejor solución y su capacidad clasificatoria; finalmente $maxiterMS$ es un parámetro previamente definido que indica cuantas iteraciones deben transcurrir sin mejorar f^{best} para que el método finalice.

A continuación, se explican los procedimientos $Constructive$ y $TabuSearch$. El procedimiento Constructive comienza con $S = \emptyset$, en cada paso elige un elemento de $v_{j^*} \in V - S$ entre los que mayor capacidad clasificatoria darían lugar si se añadieran a S, i.e. $f(S \cup \{v_{j^*}\})$ y se añade a S. El proceso finaliza cuando $|S| = p$. El pseudocódigo 2 muestra el procedimiento $Constructive$.

Procedure $Constructive(\alpha;$ output: $S)$

1. Hacer $S = \emptyset$

Repeat

2. $\forall v_j \in V - S$: calcular $g(j) = f(S \cup \{v_j\})$
3. Determinar: $gmin = min\{g(j) : v_j \in V - S\}$

$$gmax = max\{g(j) : v_j \in V - S\}$$

4. Construir $L = \{ j : v_j \in V - S, g(j) \geq \alpha \cdot gmax + (1 - \alpha) \cdot gmin \}$
5. Elegir aleatoriamente $j^* \in L$
6. Hacer $S = S \cup \{v_{j^*}\}$

until $|S| = p$

Pseudocode 2. $Constructive$ procedure

El procedimiento es relativamente sencillo. Inicialmente se hace $S = \emptyset$; en los pasos siguientes para los elementos v_j que no estén en S se calcula la capacidad de clasificatoria de S si se añadiera v_j ($g(j) = f(S \cup \{v_j\})$); a continuación, se forma una lista de candidatos L con los índices con mayor valor $g(j)$ y se elige uno de ellos aleatoriamente (j^*); la correspondiente variable v_{j^*} se añade a S. El parámetro α regula el tamaño de L. Toma valores entre 0 y 1, de forma que si $\alpha = 0$ entonces $L = \{ j : v_j \in V - S\}$ y el proceso es totalmente aleatorio; por otro lado, si $\alpha = 1$ entonces L está formado solamente por el índice j correspondiente a $gmax$ y el proceso es determinístico. Es importante elegir un valor adecuado para α que permita obtener soluciones diversas se buena calidad.

La búsqueda tabú (439) es una estrategia metaheurística que en su versión básica consiste en un procedimiento de búsqueda vecinal. En cada paso se analizan todos los movimientos posibles que se pueden realizar desde la solución actual y se ejecuta el mejor. Se consideran movimientos sencillos, de forma que cada movimiento da lugar a una solución relativamente parecida a la solución actual (solución cercana o "vecina"). El procedimiento permite

movimientos a soluciones que no mejoran la solución actual. Por otra parte, para evitar que el algoritmo cicle algunos movimientos se declaran "tabú" e inicialmente no se consideran.

En nuestro caso los movimientos consisten en intercambiar un elemento $v_j \in S$ con un elemento $v_{j'} \in V - S$. Para evitar ciclos se declara "tabú" la salida de S (durante una serie de iteraciones) de los elementos que acaban de entrar en S. De igual forma se declara "tabú" la entrada en S de los elementos que acaban de salir. Para chequear el estatus tabú de la entrada o salida de un elemento $v_j \in V$ se definen

$VectorIn(j)$: Número de la iteración en la que el elemento v_j ha entrado en S

$VectorOut(j)$: Número de la iteración en la que el elemento v_j ha salido de S.

De esta forma el intercambio de un elemento $v_j \in S$ con un elemento $v_{j'} \in V - S$ es tabú si se verifica una de estas dos condiciones

$$iter \leq VectorIn(j) + tenure \qquad (1)$$

o bien

$$iter \leq VectorOut(j') + tenure \qquad (2)$$

El parámetro $tenure$ indica el número de iteraciones en la que una salida o una entrada es tabú. La variable auxiliar $iter$ es el contador del número de iteraciones. Por otra parte, el estatus tabú de un intercambio puede ser ignorado (y por tanto el intercambio es considerado) si dicho intercambio da lugar a una solución con mayor capacidad clasificatoria que las anteriores soluciones visitadas (es lo que se denomina "criterio de aspiración"). El pseudocódigo 3 muestra el procedimiento $TabuSearch$.

Procedure $TabuSerach(tenure, maxiterTS, S;$ output: $S^*)$

1. Hacer: $S^* = S, f^* = f(S), iter = 0, iterbest = 0$

2. Hacer: $VectorIn(j) = -tenure,\ VectorOut(j) = -tenure, \quad \forall j = 1, \dots, m$

Repeat

3. Hacer $iter = iter + 1$

4. Hacer $f^b = -\infty$

   $\forall\ v_j \in S$ and $v_{j'} \in V - S$:

begin

5. Determinar el estatus tabú del intercambio (condiciones (1) y (2))

6. Determinar si el intercambio cumple el "criterio de aspiración", i.e., chequear si

$$f(S \cup \{v_{j'}\} - \{v_j\}) > f^*$$

7. Si el intercambio o bien no es tabu, o bien cumple criterio de aspiración y, además

   $f(S \cup \{v_{j'}\} - \{v_j\}) > f^b$ entonces hacer:

$$f^b = f(S \cup \{v_{j'}\} - \{v_j\}), j^b = j \text{ and } j'^b = j'$$

end

8. Hacer $S = S \cup \{v_{j'^b}\} - \{v_{j^b}\}$

9. Hacer $VectorIn(j'^b) = iter$ y $Vectorout(j^b) = iter$

10. Si $f(S) > f^*$ entonces: $S^* = S, f^* = f(S)$ and $iterbest = iter$

Until $iter > iterbest + maxiterTS$

Pseudocode 3. $TabuSerach$ procedure

Como se puede ver en el pseudocódigo 3, en cada iteración se consideran todos los intercambios que o bien no son tabú, o bien cumplen el criterio de aspiración. El mejor intercambio se almacena en las variables auxiliares j^b y j'^b. Una vez determinado el mejor intercambio, este se ejecuta y se actualizan los valores de $VectorIn(j'^b)$ y $VectorOut(j^b)$. Tras cada iteración se actualiza en su caso S^* y f^*, que son respectivamente la mejor solución

encontrada durante la búsqueda y su capacidad clasificatoria. El procedimiento finaliza cuando transcurren un numero prefijado de iteraciones ($maxiterTS$) sin mejorar S^* y f^*. En este procedimiento el parámetro $tenure$ juega un papel importante: valores altos dan lugar a que muchos movimientos sean declarados tabú y el proceso sea poco flexible; valores bajos pueden no evitar ciclos. Por tanto, una elección adecuada es crítica.

V. Descripción de los clasificadores usados

El método de selección anterior se puede combinar con diferentes clasificadores. En nuestro caso los clasificadores elegidos son ADL, RL y SVM, todos ellos lineales.

Los clasificadores lineales se basan en funciones lineales y son conceptualmente fáciles de entender. Permiten una interpretación sencilla de los resultados y, además, por lo general, son eficientes. Para su descripción usamos la nomenclatura definida arriba. Un clasificador lineal consiste en una función lineal de los valores de las variables, es decir, una función $f(\boldsymbol{x})$ de la forma

$$f(\boldsymbol{x}) = \beta_0 + \beta_1 \cdot x_1 + \beta_2 \cdot x_2 + \beta_3 \cdot x_3 + \cdots + \beta_m \cdot x_m.$$

A la función $f(\boldsymbol{x})$ se le denomina también función discriminante. Para clasificar a un individuo $\boldsymbol{x}$ se calcula el correspondiente valor $f(\boldsymbol{x})$ y si este valor es positivo se le clasifica en la clase 1, y si no se le clasifica en la clase 0. Geométricamente está función define un hiperplano en el espacio de las variables explicativas (un punto si m = 1, una recta si m =2, un plano si m = 3, etc.) Si los valores de $\boldsymbol{x}$ quedan por encima del hiperplano se clasifican en la clase 1, y sino en la clase 0. A este hiperplano también se le llama *hiperplano separador*. Por tanto, el clasificador viene definido por el vector de valores

$$\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2, \beta_3 \cdots, \beta_m)'.$$

Para calcular este vector $\boldsymbol{\beta}$ existen diferentes estrategias que dan lugar a diferentes clasificadores. A continuación, se describen los tres que vamos a emplear.

VI. Análisis discriminante

El análisis discriminante usa la idea de la descomposición de la varianza. Geométricamente se basa en buscar un vector (en el espacio de las variables explicativas) de forma que al proyectar los puntos de X se maximice la varianza entre-grupos (la separación entre los puntos medios de cada clase) y se minimice la varianza intra-grupos (la separación entre los elementos de cada clase).

Las siguientes figuras muestran esta idea. Se muestran el conjunto de entrenamiento dividido en las dos clases G_1 en azul y G_0 en marrón. Se consideran $m = 2$. Las proyecciones en el eje horizontal (x_1) y en el vertical (x_2) crean zonas de confusión (marcadas en verde) grandes. Es decir, las variables originales por si solas no sirven para discriminar bien. Sin embargo, eligiendo un nuevo eje de forma adecuada las proyecciones tienen una zona de confusión muy pequeña. La perpendicular a dicho eje en el punto adecuado es la recta de separación que estamos buscando

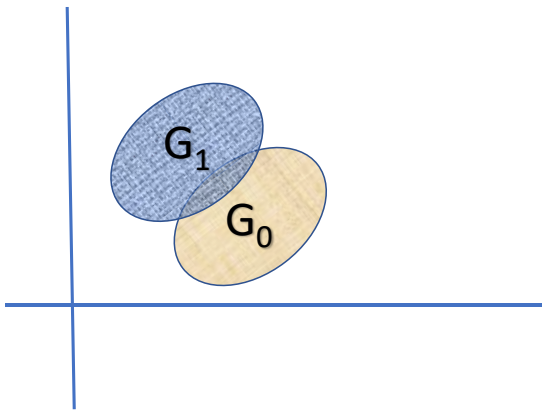

Figura 15. Los individuos del conjunto del entrenamiento divididos en G_1 y G_0

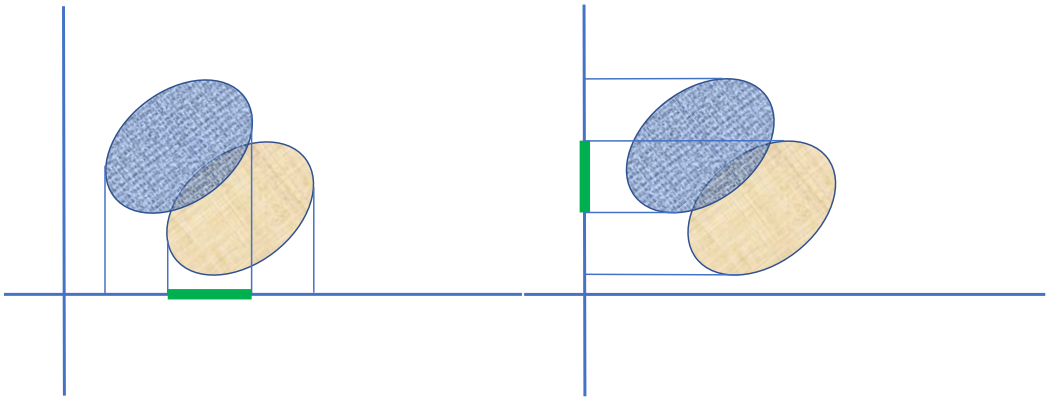

Figura 16. las proyecciones en los ejes originales muestran zonas amplias de confusión (mezcla de puntos de G_1 y G_0)

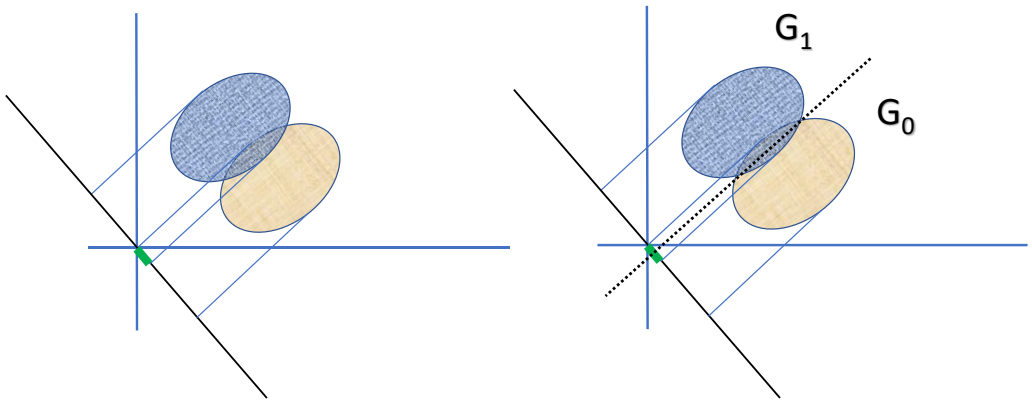

Figura 17. Nuevo eje con zona de confusión pequeña (izquierda). La perpendicular que se muestra en la derecha es el hiperplano separador que estamos buscando.

Sin entrar en un análisis formal y detallado, con este planteamiento se obtiene la siguiente función discriminante:

$$f(\boldsymbol{x}) = (\boldsymbol{\mu_1} - \boldsymbol{\mu_0})' \cdot S^{-1} \cdot \boldsymbol{x} - \left({}^{1}/_{2}\right) \cdot (\boldsymbol{\mu_1} - \boldsymbol{\mu_0})' \cdot S^{-1} \cdot (\boldsymbol{\mu_1} + \boldsymbol{\mu_0})$$

donde

- $\boldsymbol{\mu_k}$ es el vector columna formado por las medias de las variables en los elementos de la clase G_k del conjunto de entrenamiento X, para k = 0,1. A este vector se le llama *centroide* de la clase *k*;

- S es la matriz de varianzas-covarianzas de las variables en los elementos de X.

Por tanto

$$(\beta_1, \beta_2, \beta_3 \cdots, \beta_m) = (\boldsymbol{\mu_1} - \boldsymbol{\mu_0})' \cdot S^{-1}$$

y

$$\beta_0 = -(1/2) \cdot (\boldsymbol{\mu_1} - \boldsymbol{\mu_0})' \cdot S^{-1} \cdot (\boldsymbol{\mu_1} + \boldsymbol{\mu_0}).$$

VII. Regresión logística

La idea de estos modelos es estimar la probabilidad p de pertenencia de un individuo x al grupo G_1. Una vez que se estima esta probabilidad p la regla de clasificación es la siguiente: Si $p > ½$ entonces a x se le clasifica en la clase G_1; en caso contrario se le clasifica en la clase G_0.

Por otra parte, esta probabilidad se calcula como

$$p = \frac{1}{1 + e^{-z}}$$

donde z es una función lineal de los valores de las variables para x, es decir

$$z = \beta_0 + \beta_1 \cdot x_1 + \beta_2 \cdot x_2 + \beta_3 \cdot x_3 + \cdots + \beta_m \cdot x_m.$$

Obsérvese que

$$p > \tfrac{1}{2} \Leftrightarrow z > 0.$$

En efecto:

$$p > \tfrac{1}{2} \Leftrightarrow e^{-z} < 1 \Leftrightarrow z > 0.$$

Por tanto, si $z = \beta_0 + \beta_1 \cdot x_1 + \beta_2 \cdot x_2 + \beta_3 \cdot x_3 + \cdots + \beta_m \cdot x_m > 0$ entonces a x se le clasifica en la clase 1. Es decir, el clasificador creado de esta forma es lineal.

La función

$$g(z) = \frac{1}{1 + e^{-z}}$$

se le denomina función logística. Es una función creciente y sirve para transformar valores de z en toda la recta real, al intervalo (0,1), según indica la figura 18.

Por tanto, esos valores transformados ya pueden ser considerados como estimaciones de probabilidad. Obsérvese que valores muy bajos de z dan lugar a probabilidades bajas

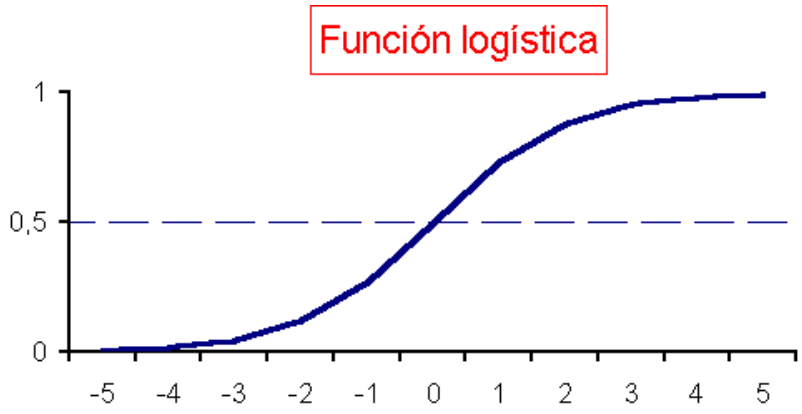

Figura 18. Función logística

Para cada individuo $\boldsymbol{x_i}$ del conjunto de entrenamiento esta probabilidad de pertenencia al grupo G_1 la denotamos por p_i. Por tanto

$$p_i = \frac{1}{1 + e^{-z_i}}$$

donde

$$z_i = \beta_0 + \beta_1 \cdot x_{i1} + \beta_2 \cdot x_{i2} + \beta_3 \cdot x_{i3} + \cdots + \beta_m \cdot x_{im}.$$

Para estimar el vector de coeficientes $\boldsymbol{\beta}$ se hace uso de lo que se denomina el criterio de máxima verosimilitud. Esto equivale en este caso a determinar cuáles son los valores del

vector $\boldsymbol{\beta}$ que hacen que se maximice la probabilidad conjunta de que los individuos de entrenamiento X pertenezcan cada uno a su clase. Si se supone independencia entre los individuos, esta probabilidad conjunta es el producto de las probabilidades individuales. Por otra parte, obsérvese que la probabilidad de que cada individuo xi pertenezca a su clase se pude expresar como

$$p_i{}^{y_i} \cdot (1 - p_i)^{1-y_i}.$$

En efecto, si $\boldsymbol{x_i} \in G_1$, entonces $y_i = 1$ y la probabilidad de pertenecer a su grupo es la probabilidad de pertenecer a G_1, es decir p_i, luego en este caso

$$p_i{}^{y_i} \cdot (1 - p_i)^{1-y_i} = p_i;$$

de la misma forma si $\boldsymbol{x_i} \in G_0$, entonces $y_i = 0$ y la probabilidad de pertenecer a su grupo es a probabilidad de pertenecer a G_0, es decir $1 - p_i$, luego en este caso

$$p_i{}^{y_i} \cdot (1 - p_i)^{1-y_i} = 1 - p_i.$$

Por tanto, la probabilidad conjunta de que los individuos de X pertenezcan cada uno a su clase se puede expresar como

$$L = \prod_{i=1}^{n} p_i{}^{y_i} \cdot (1 - p_i)^{1-y_i}$$

A L se le denomina *función de verosimilitud*. Obsérvese que L es función de los valores de p_i, que a su vez son función de los correspondientes z_i y estos a su vez son función del vector $\boldsymbol{\beta}$. Por tanto, L es función de $\boldsymbol{\beta}$. Se trata de buscar los valores de $\boldsymbol{\beta}$ que maximizan L. No obstante, los valores que maximizan L maximizan también su logaritmo neperiano, que es como sigue

$$\ln(L) = \sum_{x_i \in G_1} \ln p_i + \sum_{x_i \in G_0} \ln(1 - p_i).$$

Habitualmente se usa $\ln(L)$ para determinar los valores de $\boldsymbol{\beta}$ ya que tiene una expresión y unas derivadas más sencillas. Se suelen usar variantes de métodos como el de Newton, gradiente conjugado o descenso coordinado. Aún con todo, su cálculo es mucho más complicado y requiere más recursos computacionales que en el análisis discriminante.

VIII. Máquina de vector soporte

La Máquina de vector soporte es también conocida por su acrónimo en inglés, SVM (Support Vector Machine). Para entender mejor la idea en la que se basan, vamos a suponer, en primer lugar, el caso en el que las clases G_1 y G_0 son separables linealmente en el conjunto de entrenamiento, como en el caso que se muestra la figura 5. La idea no es sólo encontrar un hiperplano (recta en este caso) que separe las dos clases sino encontrar el hiperplano que mejor los separe.

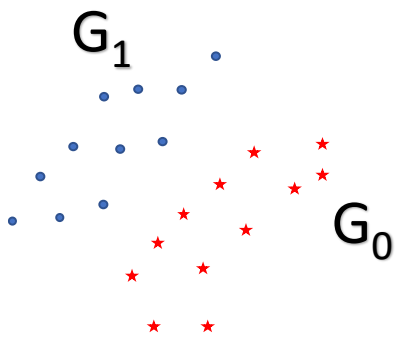

Figura 19. Dos clases que se pueden separar linealmente

Así en la figura 6 se muestra una recta que no consigue separar las dos clases. En la figura 7 se muestra una recta que si consigue separar ambas clases. Pero se observan casos de ambas clases tocando esa "frontera". Esto da la sensación de "poca robustez", es decir, es posible que puedan existir varios casos (ya fuera del conjunto de entrenamiento) con valores próximos a estos puntos "fronterizos", que traspasen esa recta, y por tanto sean clasificados en la clase incorrecta.

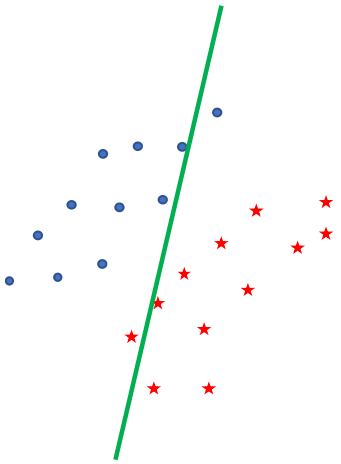

Figura 20. Hiperplano que no separa las dos clases

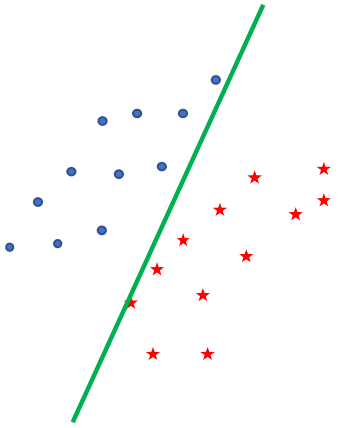

Figura 21. Hiperplano que si separa las dos clases

Por tanto, lo ideal es encontrar una recta que no sólo separe ambas clases, sino que los elementos de cada clase queden lo más alejados posible de esta recta. La figura 8 muestra una recta que cumple este requisito. Además, se puede observar (también en la figura 9) como existe una franja "vacía" alrededor de esta recta.

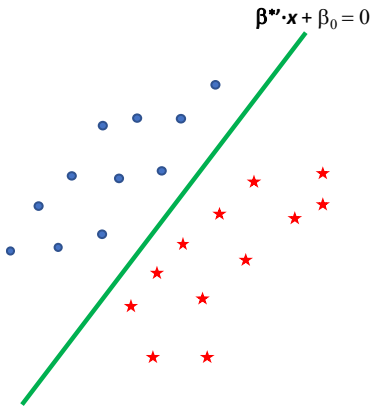

Figura 22. Hiperplano que separa las dos clases de forma más "robusta"

El problema por tanto trata de encontrar un hiperplano separador que maximice el ancho de esta franja como se muestra en la figura 9. Para formalizar este problema denotamos por $\boldsymbol{\beta}^* = (\beta_1, \beta_2, \beta_3 \cdots, \beta_m)'$. El hiperplano que buscamos es de la forma $\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{x} + \beta_0 = 0$. La franja vacía viene delimitada por los hiperplanos paralelos $\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{x} + \beta_0 = +1$ y $\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{x} + \beta_0 = -1$. La distancia $\boldsymbol{\gamma}$ entre estos dos hiperplanos es el ancho de la franja vacía. Se puede demostrar que $\boldsymbol{\gamma} = {}^{2}\Big/{\sqrt{\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{\beta}^*}}$. Por tanto, maximizar $\boldsymbol{\gamma}$ equivale a minimizar $\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{\beta}^*$. Por otra parte, se exige que los individuos de X no estén en la zona vacía, es decir, que los pertenecientes a la clase G_1 estén por "encima" del hiperplano $\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{x} + \beta_0 = +1$, y los pertenecientes a la clase G_0 estén por "debajo" del hiperplano $\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{x} + \beta_0 = -1$.

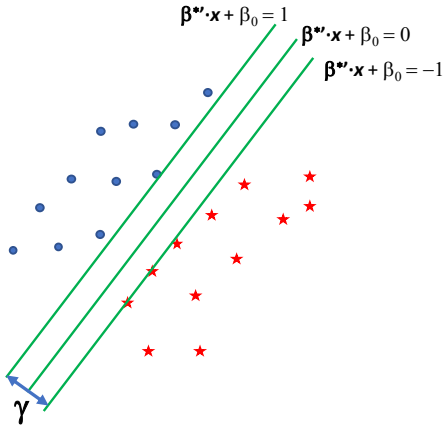

Figura 23. Ilustración gráfica del problema

Por tanto, el problema se puede definir como

$$\min_{\boldsymbol{\beta}^*,\beta_0} \boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{\beta}^*$$

sujeto a:

$$\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{x} + \beta_0 \geq +1, \ \forall x_i \in G_1$$

$$\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{x} + \beta_0 \leq -1, \ \forall x_i \in G_0$$

Este es la descripción general del fundamento de los modelos SVM cuando las dos clases son separables linealmente. Sin embargo, en la realidad en la mayoría de las aplicaciones esto no es lo habitual. Por tanto, no tiene sentido la búsqueda de un hiperplano que los separe perfectamente. Sin embargo, el planteamiento anterior puede aprovecharse. La idea es modificarlo permitiendo que algunos puntos puedan estar en la zona "vacía", es decir que algunos puntos de G_1 estén por "debajo" de $\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{x} + \beta_0 = +1$, y que algunos puntos de G_0 estén por "encima" de $\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{x} + \beta_0 = -1$. Para ello se introducen unas variables $\varepsilon_i, \forall i = 1, \ldots, n$. Estas variables ε_i miden este "error" o desviación, en el caso de producirse, para cada punto x_i. La figura 10 ilustra esta situación. Obsérvese como hay 3 puntos que sobrepasan el límite de su hiperplano: 2 de la clase G_1 y 1 de la clase G_0. Por tanto, las deviaciones correspondientes a estos 3 puntos verifican $\varepsilon_i > 0$. También se observa como

el punto de la clase G_0 sobrepasa incluso el hiperplano $\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{x} + \beta_0 = 0$, por tanto, en este caso la correspondiente desviación verifica que $\varepsilon_i > 1$.

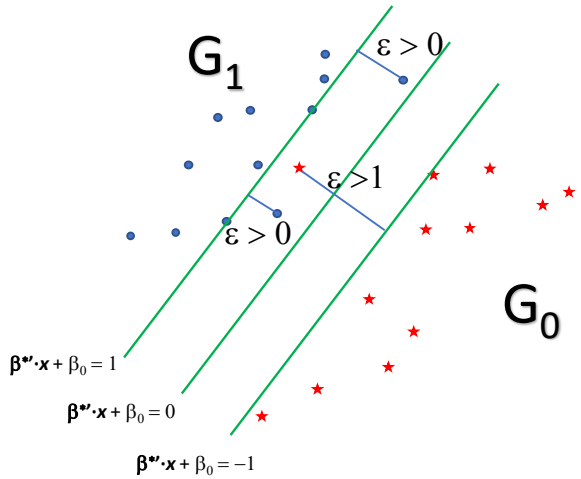

Figura 24. Dos clases que no se pueden separar linealmente

Las variables ε_i se introducen tanto en la función objetivo como en las restricciones. El modelo modificado se plantea como sigue

$$\min_{\boldsymbol{\beta}^*, \beta_0, \varepsilon_i} \boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{\beta}^* + C \cdot \sum_{i=1}^{n} \varepsilon_i$$

sujeto a:

$$\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{x} + \beta_0 + \varepsilon_i \geq +1, \ \forall x_i \in G_1$$

$$\boldsymbol{\beta}^{*\prime} \cdot \boldsymbol{x} + \beta_0 - \varepsilon_i \leq -1, \ \forall x_i \in G_0$$

$$\varepsilon_i \geq 0, i = 1, .., n$$

En la función objetivo C es un parámetro que sirve para penalizar las desviaciones. La elección del valor de C es crítico ya que valores altos evitan errores en el conjunto de entrenamiento pueden dar lugar a sobreajuste. Mientras que valores bajos, permiten muchos errores en el conjunto de entrenamiento, con lo cual el ajuste es malo. Un valor adecuado puede dar lugar modelos robustos que eviten ambos problemas.

PRUEBAS COMPUTACIONALES

En esta sección se van a realizar diferentes pruebas computacionales. Un primer grupo de pruebas van a servir para realizar el ajuste de parámetros del método propuesto. Un segundo grupo de pruebas van a servir para comparar nuestro método con otros populares métodos de selección de variables en la literatura reciente sobre este tema. Vamos a intentar demostrar que nuestro método, en general, no solo compite, sino que obtiene mejores resultados considerando diferentes parámetros. Para ello se van a usar diferentes bases de datos, todas ellas sobre diagnóstico en medicina

Para realizar estas pruebas se usan 6 bases de datos: 5 de ellas pertenecen al conocido repositorio de la UCI (University of California in Irvine), la sexta es la base datos que se presenta en este trabajo sobre diagnosis de Alzheimer. Al tratarse de bases de datos sobre diagnosis, las clases son 2 (tiene la enfermedad / no la tiene). A continuación, se muestra la descripción de las diferentes bases de datos y sus características.

Tabla 21. Bases de datos usadas

Nombre	Casos	Variables	Observaciones
Parkinson	195	22	
Quality Assessment of Digital Colposcopies (QADC)	287	67	
SPECTF Heart	267	44	
WISCONSIN BREAST CANCER -Diagnostic (WDBC)	569	30	
WISCONSIN BREAST CANCER -Prognostic (WPBC)	198	31	Se elimina una variable con 3 casos perdidos
Olalla Alzheimer's disease	1548	28	Vazquez OS. Database Alzheimer 2023. osf.io/b6259.

Nota: La información acerca de la base de datos usada se puede consultar en la siguiente página. https://osf.io/b6259/?view_only=8903fdf906b2487b8d69e36371c70919

El ajuste de parámetros se lleva a cabo usando un conjunto de 18 instancias. Estas instancias son el resultado de combinar cada una de las seis bases de datos con los siguientes valores de p (tamaño del subconjunto de variables), p = 3 (subconjuntos muy pequeños), 7 (subconjuntos pequeños) y 12 (subconjuntos medianos).

Como ya se ha comentado, nuestro método $MultiStartTabu$ (MST) consta de 4 parámetros: α, $tenure$, $maxiterTS$ and $maxiterMS$. El parámetro α indica el grado de aleatoriedad del procedimiento constructivo, y el parámetro $tenure$ regula el número de movimientos "tabú" en el procedimiento $TabuSearch$. Los parámetros $maxiter$ y $maxiterMS$ se utilizan como criterios de parada en el procedimiento tabú y en el procedimiento general de EM. Para ajustar los otros dos parámetros (α and $tenure$), se fijan los valores $maxiter = 10 \cdot n$ y $maxiterMS = 20$. Para α, se considera el valor α = 0, 0.1, 0.5, 0.9, 0.99 y 1. El valor de $tenure$ considerado fue $tenure = {}^{n}/_{2}, n, 2 \cdot n$ y $5 \cdot n$. De todas las combinaciones, la que dio mejores resultados fue α = 0.99 y $tenure = {}^{n}/_{2}$. Con estos valores se analizó $maxiter$ and $maxiterMS$. Se determinó que no había mejoras significativas con valores superiores a $maxiterTS = 10 \cdot n$ y $maxiterMS = 10$. Por lo tanto, estos valores se utilizaron en el resto de las pruebas.

I. Comparación con otros métodos

Algoritmos frente a los que nos comparamos

En esta subsección vamos a comparar con los siguientes métodos para wrapper feature selection:

- Algoritmos Genéticos (410,411). Los algoritmos genéticos (AG) se han aplicado con éxito a la selección de características. La selección de grupos de características se puede realizar de manera eficiente mediante el uso de AG, ya que exploran el espacio de soluciones y explotan las regiones más prometedoras sin realizar una búsqueda exhaustiva(402).
- Grey Wolf Optimizer (GWO) (412,440). GWO: Se utiliza en el dominio de selección de características para encontrar un subconjunto de características que maximice la precisión de la clasificación mientras minimiza el número de características

seleccionadas (412). Grey Wolf Optimizer (GWO) es un algoritmo reciente que se ha empleado con éxito para resolver problemas de selección de características (419).

- Particle Swarm Optimization (PSO): Concretamente se usa el método propuesto por Xue et al. (409). Consiste en una técnica de computación evolutiva eficiente. Se utiliza esta técnica con el fin de desarrollar nuevos enfoques de selección de características y de esta manera, maximizar el rendimiento de la clasificación, minimizar el número de características y reducir el tiempo computacional(409).
- Whale Optimization Algorithm (418,419). Whale optimization: WOA es un algoritmo evolutivo que imita el comportamiento de búsqueda de alimento de las ballenas jorobadas en la naturaleza (419). WOA pertenece a la familia de algoritmos estocásticos basados en población propuestos por Mirjalili y Lewis en 2016 (441).
- Flower Pollination Algorithm (FPA): Concretamente se usa el método propuesto por Sayed et al. (414) El algoritmo de polinización de flores (FPA) fue desarrollado por Xin-She Yang en 2012 (442). Inspirado en el proceso de polinización de las flores de las plantas con flores(413). Se ha extendido a problemas de optimización multiobjetivo y se ha encontrado que es muy eficiente(414).

Estos métodos, a diferencia del nuestro, no resuelven el problema de selección de variables para un valor de p fijo o predeterminado: lo que buscan es un subconjunto de variables con equilibrio entre el porcentaje de aciertos y su tamaño. Para ello usan como función objetivo la siguiente

$$g(S) = \beta \cdot f(S) + (1 - \beta) \cdot (1 - \frac{|S|}{m})$$

la primera parte de la función objetivo hace referencia a la ratio de aciertos, y la segunda al tamaño del subconjunto.

Por tanto, para una mejor comparativa con estos métodos adaptamos nuestro método: resolvemos el mismo para diferentes valores de p, desde 1 hasta un valor máximo $maxp$. Concretamente se toma $maxp = 0.6 \cdot m$, (redondeando al entero más próximo). Una vez obtenidas las $maxp$ soluciones (es decir subconjuntos S, uno por tamaño) elegimos la mejor según la función g.

Diseño de las pruebas

Para poder, no solo comparar los resultados obtenidos por los diferentes métodos, si no realizar tests y poder obtener conclusiones estadísticas, vamos a seguir un diseño de validación cruzada de k pliegues (en inglés k-folder cross-validation). Este diseñó consiste en partir cada base de datos en k partes o pliegues, (nosotros usaremos k = 10). Se elige un pliegue que denominamos conjunto de test T_1 y con los 9 pliegues restantes unidos se obtiene el que denominamos conjunto de entrenamiento E_1. A continuación, se elige otro pliegue diferente a T_1 que da lugar al conjunto de test T_2 y con los 9 pliegues restantes unidos se obtiene el conjunto de entrenamiento E_2, y así sucesivamente. De esta forma con los 10 pliegues iniciales, se obtienen 10 conjuntos de entrenamiento (E_1, E_2, E_3 ...) y 10 conjuntos test (T_1, T_2, T_3 ...). La figura 25 ayuda a explicar este proceso.

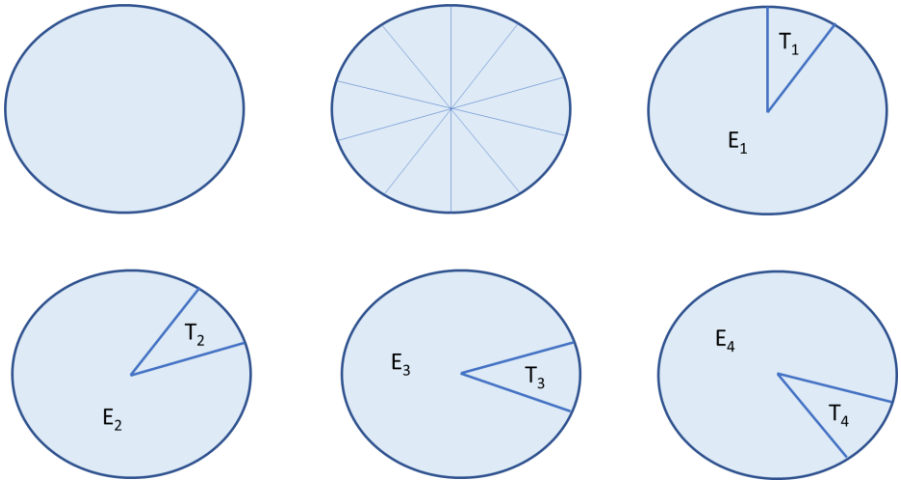

Figura 25. Validación cruzada: obtención de los 10 pares entrenamiento validación

Obsérvese que de esta forma cada conjunto de entrenamiento y su correspondiente conjunto test están formados por casos diferentes (los casos de E_1 y T_1 son diferentes, lo mismo que E_2 y T_2, etc). De esta forma se pude analizar si los modelos obtenidos por los conjuntos de entrenamiento mantienen la calidad y la precisión cuando tienen que clasificar casos diferentes a aquellos con los que se han creado.

Una vez obtenido estos 10 pares de conjuntos entrenamiento-test (E_1-T_1, E_2-T_2, E_3-T_3, …) para cada base datos, y para cada clasificador (ADL, RL, SVM) se realizan las pruebas de la siguiente forma:

Para cada método se obtiene un modelo con cada uno de los conjuntos de entrenamiento. Cada uno de estos modelos viene definido por las variables seleccionadas y los correspondientes coeficientes. Con el modelo obtenido, calcular diferentes métricas de desempeño o de calidad de dicho clasificador tanto en el conjunto de entrenamiento como en el correspondiente conjunto test.

- Una vez que se han obtenido los 10 modelos por el método (uno por conjunto de entrenamiento), obtener los estadísticos de las anteriores métricas. En este caso media y varianza.

- Cuando se han ejecutado todos los métodos (cada uno de ellos con los 10 conjuntos de entrenamiento) se pueden realizar diferentes tests (t-tests) para comparar las diferentes métricas entre diferentes pares de métodos.

La figura 26 muestra este proceso.

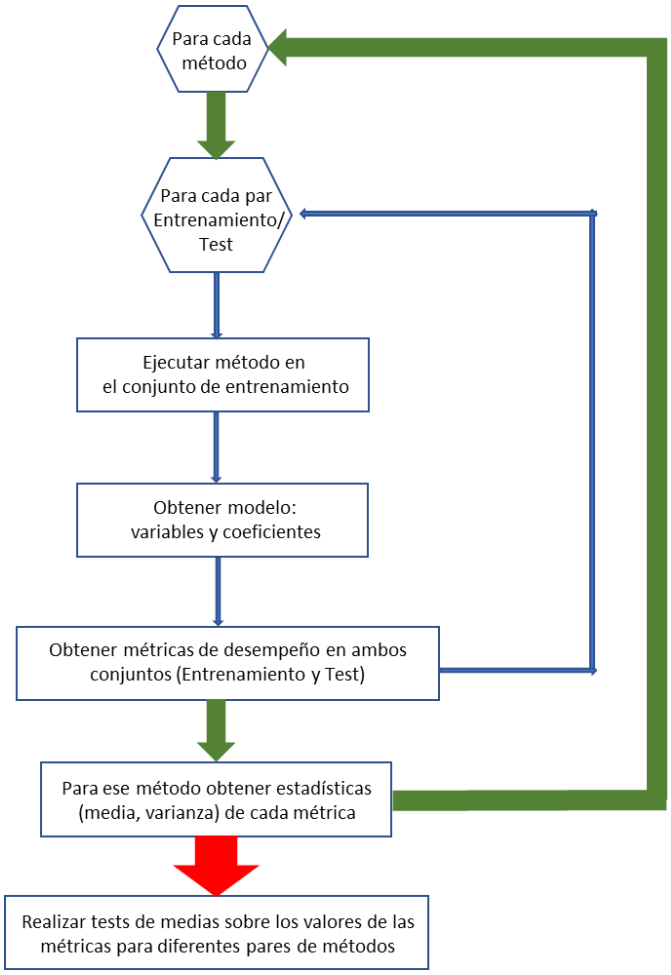

Figura 26. Proceso de las pruebas con el diseño de validación cruzada para cada base de datos y para cada clasificador

Para explicar las métricas que se van a usar, previamente se definen los siguientes parámetros. Sea un modelo de clasificación binario (como en el caso de diagnosis) aplicado a un conjunto de datos se define

- TP ("*true positives*"): número de casos reales positivos bien clasificados

- TN ("*true negatives*"): número de casos reales negativos bien clasificados

- FP (“*false positives”*): número de casos reales positivos mal clasificados

- FN (“*false negatives”*): número de casos reales negativos mal clasificados

Con estas definiciones las métricas que se van a usar son las siguientes

- $ACC\ (Accuracy) = \frac{TP+TN}{TP+FP+TN+FN}$

- $AUC\ (Area\ Under\ Curve) = \left(1 + \frac{TP}{TP+FN} - \frac{FP}{TN+FP}\right)\Big/_2$

- $Gmean\ (Geometric\ Mean) = \sqrt{\frac{TP}{TP+FN} \cdot \frac{TN}{TN+FP}}$

- $F1\ (F1\ Score) = \frac{2 \cdot TP}{2 \cdot TP+FP+FN}$

Obsérvese que la métrica ACC cuando el conjunto de datos es el conjunto de entrenamiento X, coincide con la función de fitness f definida anteriormente. Por otra parte, las otras 3 métricas también son muy usadas y son muy útiles cuando los conjuntos de reales positivos y reales negativos están poco “balanceados” o equilibrados.

RESULTADOS

A continuación, se van a mostrar los resultados obtenidos por los diferentes métodos para cada clasificador y cada base de datos. La tabla 22 muestra las estadísticas referidas a la métrica ACC, tanto en los conjuntos de entrenamiento y test usando como clasificador ADL. Los resultados de la métrica se expresan en % (es decir, se han multiplicado x 100). Esta tabla se organiza de la siguiente forma:

- Tiene dos partes, la parte de arriba se refiere a los resultados en los conjuntos de entrenamiento y la de abajo a los resultados en los conjuntos test.

- Cada fila muestra los resultados de los diferentes métodos en cada base de datos. Concretamente se muestra la media y la desviación típica muestral de ACC en los 10

conjuntos (entrenamiento o test según el caso). Así por ejemplo nuestro método MST obtiene en los conjuntos de entrenamiento un ACC medio de 83.82 (%) con una desviación típica de 1.75. Los mejores resultados medios para cada base de datos están marcados en negrita

- En base a estas medias y desviaciones de cada método, se realizan tests de medias para cada base de datos. Concretamente se realizan tests de contraste de medias bilaterales (tests de la t de Student es decir t-tests) entre nuestro método MST y cada uno de los otros 5 métodos, con una significación del 5%. Si la diferencia es significativa a favor de nuestro método se muestra un "+" tras los resultados del método con el que se compara; si la diferencia no es significativa se muestra un "="; si la diferencia es significativa a favor del otro método se muestra un "-". Así por ejemplo el t-test que compara los resultados de nuestro método MST (media 83.82 y desviación típica 1.75), con el método GA (media 81.02 y desviación típica 2.57) en la base de datos *Parkinson* se concluye que esta diferencia es significativa a favor de nuestro método.

- El resumen de los resultados de los t-tests se muestra en la fila final de cada una de las dos partes (fila "*Resumen tests (W/T/L)*"). En dicha fila se indica el número de "Victorias" (Wins, W), "Empates" (Ties, T) y "Derrotas" ("Loses", L) de nuestro método con cada uno de los 5 métodos con los que se ha comparado en las 6 bases de datos. (Las "Victorias" son las diferencias significativas a favor de nuestro método y de forma análoga se definen los "Empates" y las "Derrotas"). Así, por ejemplo, en el conjunto de entrenamiento nuestro método ha obtenido 6 "Victorias", 0 "Empates" y 0 "Derrotas" frente a GA. Es decir que en las 6 bases de datos consideradas las diferencias a favor de nuestro método frente a GA son significativas.

Tabla 22. Resultados de ACC (%) usando como clasificador Análisis Discriminante

	MST	***GA***	***GWO***	***PSO***	***WOA***	***FPA***
Training Set						
Parkinson	**83.82±1.75**	81.02±2.57 (+)	82.39±2.05 (+)	80.34±1.87 (+)	79.37±2.18 (+)	79.77±2.11 (+)
QADC	**80.18±1.52**	79.37±1.44 (+)	79.25±1.53 (+)	78.09±1.50 (+)	77.86±1.77 (+)	78.05±1.70 (+)
SPECTF Heart	**79.69±1.41**	77.74±1.03 (+)	78.90±1.39 (+)	77.49±1.46 (+)	76.16±1.99 (+)	76.61±2.12 (+)
WDBC	**96.55±0.23**	96.02±0.46 (+)	96.21±0.21 (+)	95.68±0.37 (+)	95.37±0.91 (+)	96.02±0.46 (+)
WPBC	**79.07±2.74**	77.05±2.83 (+)	77.83±3.07 (=)	77.55±2.44 (+)	73.68±3.61 (+)	73.51±3.81 (+)
Olalla Alzheimer	**79.88±3.40**	76.66±2.03 (+)	77.88±3.30 (+)	75.96±2.46 (+)	75.12±0.86 (+)	75.57±0.65 (+)
Resumen tests (W/T/L)		*6/0/0*	*5/1/0*	*6/0/0*	*6/0/0*	*6/0/0*
Test Set						
Parkinson	**81.55±2.50**	78.45±2.24 (+)	80.50±2.23 (=)	77.47±2.15 (+)	76.89±2.90 (+)	77.95±2.41 (+)
QADC	**78.76±2.44**	77.34±2.55 (+)	78.07±2.69 (=)	75.96±1.90 (+)	76.64±2.49 (+)	76.65±2.36 (+)
SPECTF Heart	**79.02±2.01**	77.15±1.15 (+)	78.63±2.00 (=)	77.14±1.47 (+)	76.03±2.61 (+)	76.41±2.41 (+)
WDBC	**95.96±0.84**	95.26±0.84 (+)	95.43±0.90 (+)	95.08±1.10 (+)	94.56±1.28 (+)	95.26±0.84 (+)
WPBC	**77.76±3.59**	76.26±3.36 (=)	77.26±4.30 (=)	**77.76±2.71** (=)	72.74±4.80 (+)	72.24±4.80 (+)
Olalla Alzheimer	**79.01±3.40**	75.45±2.09 (+)	76.87±3.27 (+)	75.00±2.38 (+)	74.10±0.90 (+)	74.35±0.57 (+)
Resumen tests (W/T/L)		*5/1/0*	*2/4/0*	*5/1/0*	*6/0/0*	*6/0/0*

Nota: MST: multistartTabu; GA: Genetic Algorithm; GWO: Grey Wolf optimizier; PSO: particle swarm optimization; WOA: whale optimization algorithm; FPA: flower pollination algorithm

De la tabla 22 se puede observar que:

- En todas las bases de datos y tipos de conjunto (entrenamiento o test) nuestro método obtiene mejores resultados medios. Además, en la mayoría de los casos estas diferencias son significativas.

- Si observamos a los resultados en los conjuntos de entrenamiento solamente en un caso (el test frente a *GWO* en la base de datos WPCB) de las 30 combinaciones posible no hay una diferencia significativa en las medias.

- En lo referido a los conjuntos test sigue habiendo una mayoría de diferencias significativas, aunque hay un mayor número de casos donde estas diferencias no lo son (6 de 30). En concreto en los t-tests frente a *GWO*, nuestro método "empata" en 4 bases de datos y "gana" en 2. En general, parece que el método *GWO* es el que obtiene resultados algo más similares a nuestro *MST*.

De igual forma, se han realizado los mismos cálculos (media, desviación típica y t-tests) para las otras métricas consideradas (*ACU*, *Gmean* y *F1*), así como para la función objetivo g (que como se ha comentado es la que guía el proceso de selección de los diferentes métodos). Para abreviar los resultados, la tabla 23 muestra el resumen de los t-tests correspondientes a cada una de las métricas (tanto en los conjuntos de entrenamiento como en los conjuntos tests), así como para la función objetivo g. La primera fila muestra los resultados para la función objetivo g el resto de filas muestran los resultados para cada una de las métricas. Concretamente se muestran el número de "Victorias", "Empates" y "Derrotas" de nuestro método frente a cada uno de los otros métodos, para dicha métrica o función (siguiendo el mismo formato de terna *W/T/L*). Tras las filas de las métricas en el conjunto de entrenamiento se añade una fila ("*Total (W/T/L)*") con el número total de "Victorias", "Empates" y "Derrotas" de nuestro método frente a cada uno de los otros métodos en el total de las 4 métricas. La misma fila se añade tras las métricas en los conjuntos test.

Tabla 23. Resumen de los t-test para las diferentes métricas con Análisis Discriminante

	GA	***GWO***	***PSO***	***WOA***	***FPA***
Función objetivo g	6/0/0	6/0/0	6/0/0	6/0/0	6/0/0
Metrics in Training Sets					
ACC	6/0/0	5/1/0	6/0/0	6/0/0	6/0/0
AUC	5/1/0	4/2/0	6/0/0	6/0/0	6/0/0
Gmean	5/1/0	5/1/0	6/0/0	5/1/0	6/0/0
F1	6/0/0	6/0/0	6/0/0	6/0/0	6/0/0
Total (W/T/L)	*22/2/0*	*20/4/0*	*24/0/0*	*23/1/0*	*24/0/0*
Metrics in Test Sets					
ACC	5/1/0	2/4/0	5/1/0	6/0/0	6/0/0
AUC	4/2/0	2/4/0	5/1/0	5/1/0	5/1/0
Gmean	4/2/0	2/4/0	5/1/0	5/1/0	5/1/0
F1	5/1/0	2/4/0	5/1/0	6/0/0	6/0/0
Total (W/T/L)	*18/6/0*	*8/16/0*	*20/4/0*	*22/2/0*	*22/2/0*

Nota: MST: multistartTabu; GA: Genetic Algorithm; GWO: Grey Wolf optimizier; PSO: particle swarm optimization; WOA: whale optimization algorithm; FPA: flower pollination algorithm. ACC: accuracy; AUC: area under curse; Gmean: geometric mean. W: wis; T: ties; L: loses.

Las conclusiones de la tabla 23 reproducen en gran medida las de la tabla 22:

- En la mayoría de los casos nuestro método obtiene resultados significativamente mejores que el resto de los métodos. No hay ningún caso donde haya diferencias significativas a favor de otro método.

- Esta superioridad es algo menos contundente en los conjuntos test, aunque sigue habiendo un mayor número de casos donde nuestro método es mejor. Solamente frente el método GWO nuestro método obtiene mayor número de empates que de victorias.

A continuación, se muestran las tablas 24 y 25 (con la misma estructura de las tablas 22 y 23) con los resultados usando Regresión Logística como clasificador.

Tabla 24. Resultados de ACC (%) usando como clasificador Regresión Logística

	MST	***GA***	***GWO***	***PSO***	***WOA***	***FPA***
Training Set						
Parkinson	**89.18±2.17**	87.58±1.33 (+)	87.52±1.07 (+)	87.12±1.26 (+)	87.01±1.65(+)	87.58±1.33 (+)
QADC	**84.75±1.22**	83.51±0.99 (+)	84.09±1.38 (+)	83.16±1.09 (+)	82.42±0.96 (+)	83.00±1.17 (+)
SPECTF Heart	**89.10±2.16**	87.64±1.80 (+)	88.51±2.19 (=)	87.52±2.05 (+)	85.31±2.12 (+)	86.31±2.44 (+)
WDBC	**98.57±1.00**	97.70±1.16 (+)	97.72±1.31 (+)	97.19±1.27 (+)	96.47±1.04 (+)	96.70±0.93 (+)
WPBC	**85.80±0.71**	84.40±1.33 (+)	85.02±0.71 (=)	83.56±2.01 (+)	82.71±1.42 (+)	82.94±1.48 (+)
Olalla Alzheimer	**82.19±2.14**	80.53±1.30 (+)	81.07±1.50 (+)	80.18±1.31 (+)	79.36±1.07 (+)	80.00±1.04 (+)
Resumen tests						
(W/T/L)		*6/0/0*	*5/1/0*	*6/0/0*	*6/0/0*	*6/0/0*
Training Set						
Parkinson	**87.16±3.66**	85.13±1.58 (+)	85.13±1.58 (+)	85.13±1.58 (+)	85.13±1.58 (+)	85.13±1.58 (+)
QADC	**84.68±2.33**	83.28±2.17 (+)	84.34±2.33 (=)	83.28±2.17 (+)	81.54±1.56 (+)	82.93±2.51 (+)
SPECTF Heart	**87.29±3.50**	85.80±2.16 (+)	**87.29±3.03** (=)	85.80±2.16 (+)	85.03±1.66 (+)	84.64±2.14 (+)
WDBC	**97.71±1.68**	96.31±1.55 (+)	96.31±1.55 (+)	96.31±1.55 (+)	95.43±1.23 (+)	95.96±1.45 (+)
WPBC	**86.39±2.25**	85.39±3.55 (=)	85.89±3.02 (=)	84.89±3.94 (=)	83.39±3.93 (+)	83.39±3.93 (+)

	MST	***GA***	***GWO***	***PSO***	***WOA***	***FPA***
Olalla Alzheimer	**81.20±2.15**	79.46±1.22 (+)	79.97±1.49 (+)	79.13±1.25 (+)	78.29±1.17 (+)	78.94±0.99 (+)
Resumen tests		*5/1/0*	*3/3/0*	*5/1/0*		
(W/T/L)					*6/0/0*	*6/0/0*

Nota: MST: multistartTabu; GA: Genetic Algorithm; GWO: Grey Wolf optimizier; PSO: particle swarm optimization; WOA: whale optimization algorithm; FPA: flower pollination algorithm. ACC: accuracy; AUC: area under curse; Gmean: geometric mean. W: wis; T: ties; L: loses.

Tabla 25. Resumen de los t-test para las diferentes métricas con Regresión Logística

	GA	***GWO***	***PSO***	***WOA***	***FPA***
Función objetivo			6/0/0	6/0/0	
g	6/0/0	6/0/0			6/0/0
Metrics in Training Sets					
ACC	6/0/0	5/1/0	6/0/0	6/0/0	6/0/0
AUC	5/1/0	4/2/0	5/1/0	6/0/0	6/0/0
Gmean	5/1/0	3/3/0	5/1/0	6/0/0	6/0/0
F1	6/0/0	5/1/0	6/0/0	6/0/0	6/0/0
Total (W/T/L)	*22/2/0*	*17/7/0*	*22/2/0*	*24/0/0*	*24/0/0*
Metrics in Test Sets					
ACC	5/1/0	3/3/0	5/1/0	6/0/0	6/0/0
AUC	4/2/0	3/3/0	5/1/0	6/0/0	6/0/0
Gmean	4/2/0	3/3/0	4/2/0	6/0/0	6/0/0
F1	6/0/0	3/3/0	6/0/0	6/0/0	6/0/0
Total (W/T/L)	*19/5/0*	*12/12/0*	*20/4/0*	*24/0/0*	*24/0/0*

Nota: MST: multistartTabu; GA: Genetic Algorithm; GWO: Grey Wolf optimizier; PSO: particle swarm optimization; WOA: whale optimization algorithm; FPA: flower pollination algorithm. ACC: accuracy; AUC: area under curse; Gmean: geometric mean. W: wis; T: ties; L: loses.

Las conclusiones de las tablas 24 y 25 son muy parecidas a las obtenidas de las tablas 22 y 23: en la gran mayoría de los casos (métricas y bases de datos) nuestro método mejora significativamente los resultados de los otros métodos. Parece que en los conjuntos test estas diferencias son muy ligeramente menos significativas. Respecto al método GWO sigue siendo el que "mejor compite" con nuestro método respecto a los otros. No obstante, incluso frente a este método (GWO) en gran parte de los casos hay diferencias significativas a favor de nuestro método.

De forma análoga se muestran las tablas 26 y 27 con los resultados usando Support Vector Machine como clasificador.

Las conclusiones de las tablas 26 y 27, con SVM son prácticamente iguales a las obtenidas para los otros dos clasificadores. En definitiva, de las pruebas realizadas se puede observar que, considerando todos los clasificadores, todas las bases de datos y todas las métricas (tanto en los conjuntos de entrenamiento, como tests, así como en la función g) no hay ningún caso donde haya diferencias significativas a favor de algún de los otros métodos. Es más, en la mayoría de los casos existen diferencias significativas a favor de nuestro método. Estas diferencias significativas se dan algo más en los conjuntos de entrenamiento y algo menos en las métricas de los conjuntos test. Respecto a cada uno de los diferentes métodos con los que hemos comparado nuestro MST, el método GWO parece funcionar algo mejor que GA, PSO, WOA y FPA. En efecto, la proporción de diferencias significativas sobre este método es algo menor que con los otros (especialmente cuando el clasificador ADL). No obstante, incluso con este método todas las diferencias significativas que existen son a favor de nuestro método MST.

Tabla 26. Resultados de ACC (%) usando como clasificador Support Vector Machine

	MS	***GA***	***GWO***	***PSO***	***WOA***	***FPA***
Training Set						
Parkinson	**89.52±1.36**	87.64±1.34 (+)	88.21±0.27 (+)	87.41±1.15 (+)	87.24±1.58 (+)	87.64±1.34 (+)
QADC	**83.00±1.13**	81.53±1.10 (+)	82.42±1.17 (+)	81.03±1.45 (+)	80.41±1.09 (+)	81.07±1.34 (+)
SPECTF Heart	**87.97±1.89**	85.35±1.55 (+)	85.60±1.79 (+)	84.73±1.87 (+)	84.65±1.29 (+)	84.69±1.41 (+)
WDBC	**98.52±0.95**	97.46±0.96 (+)	97.75±1.32 (+)	97.19±1.22 (+)	96.45±0.98 (+)	96.54±0.88 (+)
WPBC	**86.59±2.08**	83.89±2.34 (+)	85.63±2.33 (=)	84.74±2.93 (+)	82.94±2.34 (+)	83.11±1.95 (+)
Olalla Alzheimer	**81.83±1.63**	79.39±1.76 (+)	80.58±1.87 (+)	79.14±2.28 (+)	77.42±2.04 (+)	78.42±1.93 (+)
Resumen tests						
(W/T/L)		*6/0/0*	*5/1/0*	*6/0/0*	*6/0/0*	*6/0/0*
Training Set						
Parkinson	**86.13±3.49**	85.13±1.58 (=)	85.13±1.58 (=)	85.13±1.58 (=)	84.61±0.42 (+)	85.13±1.58 (=)
QADC	**82.23±1.07**	79.78±2.84 (+)	81.88±1.39 (=)	79.78±2.84 (+)	78.04±1.74 (+)	80.12±2.50 (+)
SPECTF Heart	**86.52±1.86**	85.40±1.10 (+)	85.78±1.42 (=)	83.90±3.03 (+)	84.63±1.38 (+)	84.27±2.30 (+)
WDBC	**97.53±1.50**	96.13±1.12 (+)	96.31±1.55 (+)	96.31±1.55 (+)	95.43±1.23 (+)	95.60±1.25 (+)
WPBC	**86.39±3.26**	83.37±3.23 (=)	84.37±3.60 (+)	84.37±3.60 (+)	82.34±2.49 (+)	82.87±3.34 (+)

	MS	***GA***	***GWO***	***PSO***	***WOA***	***FPA***
Olalla Alzheimer	**80.88±1.64**	78.36±1.93 (+)	79.65±1.78 (+)	78.10±2.17 (+)	76.42±2.26 (+)	77.20±2.08 (+)
Resumen tests		*5/1/0*	*3/3/0*	*5/1/0*		
(W/T/L)					*6/0/0*	*5/1/0*

Nota: MST: multistartTabu; GA: Genetic Algorithm; GWO: Grey Wolf optimizier; PSO: particle swarm optimization; WOA: whale optimization algorithm; FPA: flower pollination algorithm. ACC: accuracy; AUC: area under curse; Gmean: geometric mean. W: wis; T: ties; L: loses.

Tabla 27. Resumen de los t-test para las diferentes métricas con Support Vector Machine

	GA	***GWO***	***PSO***	***WOA***	***FPA***
Función objetivo			6/0/0	6/0/0	
g	6/0/0	6/0/0			6/0/0
Metrics in Training Sets					
ACC	6/0/0	5/1/0	6/0/0	6/0/0	6/0/0
AUC	6/0/0	4/2/0	6/0/0	6/0/0	6/0/0
Gmean	6/0/0	4/2/0	6/0/0	6/0/0	6/0/0
F1	6/0/0	5/1/0	6/0/0	6/0/0	6/0/0
Total (W/T/L)	*24/0/0*	*18/6/0*	*24/0/0*	*24/0/0*	*24/0/0*
Metrics in Test Sets					
ACC	5/1/0	3/3/0	5/1/0	6/0/0	5/1/0
AUC	5/1/0	4/2/0	5/1/0	6/0/0	5/1/0
Gmean	5/1/0	4/2/0	5/1/0	6/0/0	4/2/0
F1	5/1/0	3/3/0	5/1/0	6/0/0	5/1/0
Total (W/T/L)	*20/4/0*	*14/10/0*	*20/4/0*	*24/0/0*	*19/5/0*

Nota: MST: multistartTabu; GA: Genetic Algorithm; GWO: Grey Wolf optimizier; PSO: particle swarm optimization; WOA: whale optimization algorithm; FPA: flower pollination algorithm. ACC: accuracy; AUC: area under curse; Gmean: geometric mean. W: wis; T: ties; L: loses.

Por otra parte, la programación que se ha realizado de los diferentes métodos permite registrar no solo la mejor solución global con respecto a la función objetivo g, sino la mejor solución (sub-conjunto de variables) para cada tamaño (número de variables). Como curiosidad, los 3 gráficos siguientes muestran el ACC en el conjunto test de cada una de las mejores soluciones (una por tamaño) registradas por cada método. Se muestra el ACC medio (en los 10 pliegues) para la base de datos *Parkinson*. Concretamente la figura 13 muestra la evolución para el clasificador ADL, la 13 para RL y la 14 para SVM

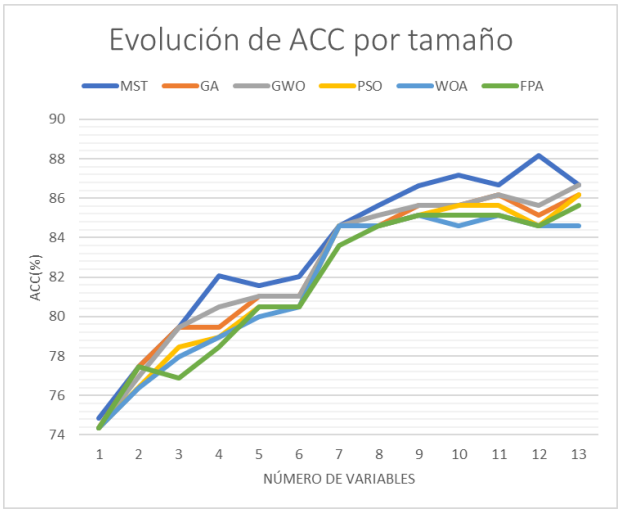

Figura 27. ACC de los diferentes métodos en conjunto test para ADL

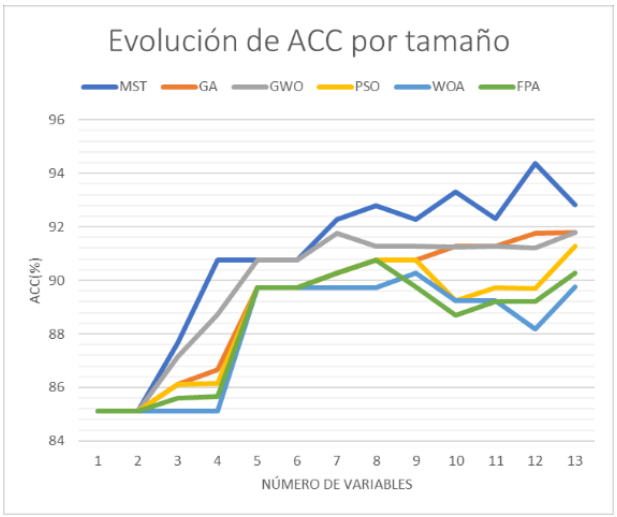

Figura 28. ACC de los diferentes métodos en conjunto test para RL

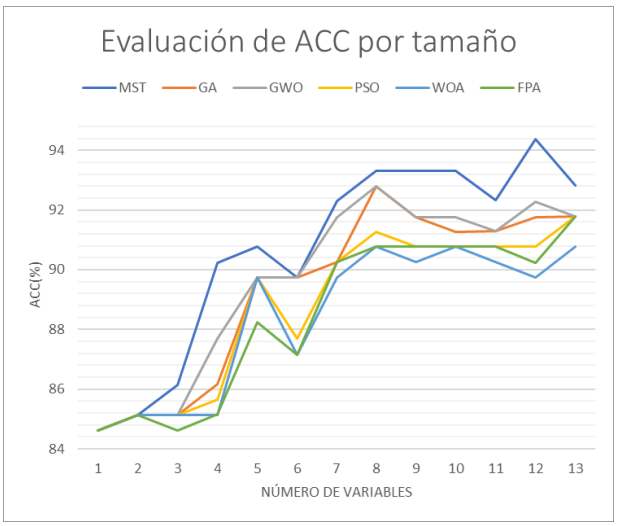

Figura 29. ACC de los diferentes métodos en conjunto test para SVM

Estos gráficos muestran el mejor desempeño de nuestro método también considerando cada tamaño de forma individual. Estas diferencias son muy pequeñas o insignificantes para tamaños muy pequeños ($p \leq 2$) pero a partir de $p = 3$ estas diferencias son más evidentes. También parece que las diferencias son mayores en RL y SVM que en ADL.

Finalmente debemos señalar algunos detalles técnicos: todos los métodos se han programado usando el lenguaje de programación Object Pascal – Delphi con el entorno de desarrollo Rad Studio 11. También con este mismo entorno se han ejecutado las diferentes pruebas. Para una mejor comparativa, para cada conjunto test que se ha considerado para las pruebas, en primer lugar, se ha ejecutado nuestro MST, con los parámetros anteriores, y después se ejecutan el resto de los algoritmos, usando estos como criterio de parada alcanzar el tiempo de computación empleado por nuestro MST. Finalmente, el ordenador usado tiene un procesador Intel Core i9-7940, 3.1 GHz y 64 Gb de RAM.

CAPÍTULO 7

"Porque hay olvidos que queman y hay memorias que engrandecen.".

(Alfredo Zitarrosa)

CAPÍTULO 7: APLICACIÓN DEL ALGORITMO QUE DETECTA LA PROBABLE APARICIÓN DE LA ENFERMEDAD DE ALZHEIMER EN SU PRIMERA FASE, UTILIZANDO TÉCNICAS DE APRENDIZAJE AUTÓNOMO O MACHINE LEARNING

ABSTRACT

La enfermedad de Alzheimer (EA) es un tipo de demencia crónica, irreversible, primaria, con lesiones localizadas en la corteza cerebral y claramente relacionada con la edad. Para el diagnóstico neurológico de las demencias, se debe obtener una historia clínica detallada del usuario, un examen neurológico completo con una buena exploración física y exploración neuropsicológica. Se pretende aplicar modelos de regresión lineal a la diagnosis de enfermedades en personas mayores, a partir de matrices de datos con muchas variables y casos. Esta metodología debe ser capaz de generar modelos de diagnosis robustos y con buena fiabilidad. Tras la aplicación de los modelos, la variable ictus es considerada como la más relevante, apareciendo en todos los clasificadores y prediciendo como única variable en todos los clasificadores un 74.87%. La variable hipertensión arterial constituye una variable importante en el clasificador SVM. En cuanto a la toma de antiarrítmicos, se considera en todos los clasificadores como un factor protector. Por último, la variable ser fumador genera controversia en los distintos modelos, ya que en unos clasifica como factor protector y en otros como factor de riesgo de la EA. El diagnóstico precoz de la EA es muy importante hoy en día. Además, los métodos de diagnóstico no invasivos basados principalmente en el historial del paciente, la observación clínica y la evaluación cognitiva, podrían ayudar a controlar el desarrollo de la EA.

Keywords: Enfermedad de Alzheimer, diagnóstico precoz, variables predictivas, hipertensión arterial, antiarrítimos, fumador.

INTRODUCCIÓN

I. Definición de la Enfermedad de Alzheimer

La EA es un tipo de demencia crónica, irreversible, primaria, con lesiones localizadas en la corteza cerebral y claramente relacionada con la edad(443). Existe una forma precoz, antes de los 65 años, y una forma tardía, después de los 65 años, que es la más frecuente y que se produce en el 85% de las personas que padecen la EA (443). Consiste en una enfermedad neurodegenerativa primaria, con las propiedades sindrómicas de demencia, que se caracteriza en su forma típica por una pérdida progresiva de la memoria y de una o varias capacidades mentales, con sintomatología clínica tanto a nivel cognitivo como conductual y funcional (444). Los síntomas de la enfermedad fueron identificados por Emil Kraepelin, mientras que la neuropatología característica fue descrita por primera vez por a Alois Alzheimer en 1906.

La EA es la demencia más prevalente y el paradigma de la demencia cortical. La diferencia en el diagnóstico de la EA en referencia a otras demencias es la alteración precoz de la memoria, seguida de la alteración en la denominación y la orientación espacial, presencia de afasia, apraxia y agnosia (444). El inicio es insidioso y su curso progresivo, con presencia de fases de meseta en la evolución.

II. Envejecimiento de la población y demencia

En el siglo XX se produjo una revolución de la longevidad. La esperanza media de vida al nacer ha aumentado 20 años desde el año 1950 y llega ahora a los 83.06 años (443). Se prevé que aumente en los próximos años, sobre todo en los países en desarrollo, en los que se prevé que la población de edad se va a cuadriplicar en los próximos 50 años. En Asia y Latinoamérica, el grupo de personas de tercera edad aumentará del 8% al 15%, en África se contempla que esa proporción aumente del 5% al 6%. En Europa y América del Norte aumentará del 20% al 26% aproximadamente (443).

Según las proyecciones de población (24) publicadas en la página web del Instituto nacional de estadística, en los próximos 15 años España ganaría 2.375.776 habitantes. La esperanza de vida al nacimiento alcanzaría en el año 2033 los 82,9 años en los hombres y los 87,7 años en las mujeres, respecto a los valores actuales. La población residente en España aumentó en 34.110 personas durante el año 2021 y se situó en 47.432.805 habitantes a 1 de enero de 2022 (445).

Por tanto, la sociedad española experimenta actualmente cambios en su demografía, su población tiene un alto porcentaje de personas mayores de 65 años, un 20,09%, se trata por tanto de una población envejecida. Además, las bajas tasas de natalidad (7.1 %) y la amplia esperanza de vida (83.06 años), describe la realidad de la población en España (446). En la Figura 30, extraída de la página web del Instituto nacional de estadística (24), se muestra el este proceso de envejecimiento, donde el grupo más numeroso es el del rango de edad comprendido entre los 45 y los 49 años.

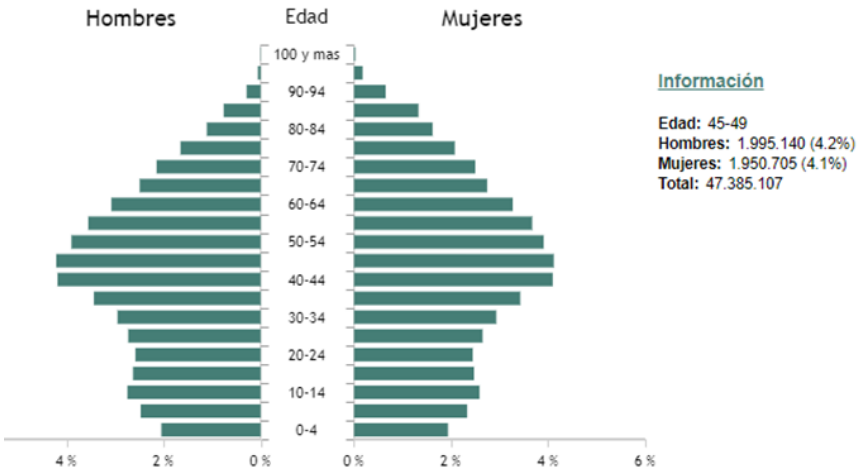

Figura 30. Pirámide de población de España entre los años 2018 y 2033

III. Visión de la enfermedad en España

La primera causa de muerte en España en el año 2020 (exceptuando las defunciones por COVID-19) fue la del grupo de enfermedades isquémicas del corazón, seguida de las enfermedades cerebrovasculares (ictus) y de las enfermedades de cáncer de bronquios y

pulmón (447). La demencia se sitúa como la cuarta causa más frecuente de defunciones en España. La EA se sitúa como la sexta causa más frecuente, con un total de 15.571 personas fallecidas (Figura 31)

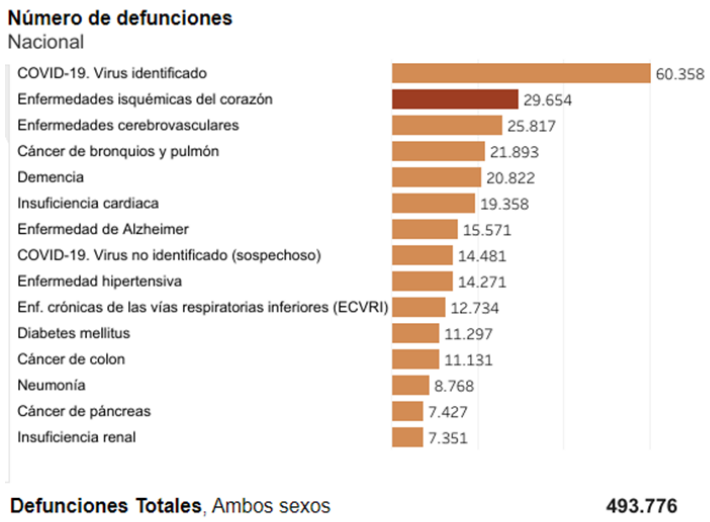

Figura 31. Causas de muerte más frecuentes en España. INE 2022

Más específicamente, si se habla de demencias, en España, el incremento de la esperanza de vida tiene como resultado que el número de personas mayores crezca de forma exponencial. Se estima que actualmente haya cerca de 800.000 personas con EA, más de la mitad en estado de dependencia. Las demencias son el problema sanitario en España que más recursos consume (448). El coste comprende por un lado los gastos directos (gasto de consultas médicas, medicación, a adaptaciones de la vivienda, ocupación de Centro de día o residencia de ancianos…) Y por otro lado los gastos indirectos (cuidadores que dedicar muchas horas de su tiempo y que reducen su productividad en el trabajo y requieren una mayor atención médica por sobrecarga, desgaste emocional de la familia ingreso del enfermo en un centro asistido, coste emocional…) (448).

Debido a todas las pluripatología que sufren las personas mayores, la institucionalización se presenta como un recurso que incluye varias opciones de estancia (centros residenciales,

servicio de estancias temporales y sistemas alternativos de alojamiento como viviendas tuteladas, servicio público de acogimiento familiar o apartamentos residenciales) (443). En este aspecto, los centros residenciales prestan atenciones durante 24 horas al día de forma permanente o temporal a personas mayores.

Las residencias de ancianos constituyen un servicio de 24 horas para personas con discapacidad, personas mayores y personas en situación de dependencia, donde se proporciona una atención individualizada e integral. En estos centros se ofrecen diferentes servicios y programas para distintas áreas de ocupación como actividades de la vida diaria, ocio y tiempo libre… Con fecha de Septiembre de 2020, el número de personas asociadas a los hogares en España supone un 4.24% de la población mayor de 65 años (449). En España hay un número total de hogares de 5.567.

IV. Los estilos de vida en las personas mayores

Para prevenir las distintas patologías que sufren las personas mayores y mejorar su calidad de vida, su estado de salud y su autonomía personal, es importante mantener un estilo de vida saludable. Esta manera, prevenir los factores de riesgo que se asocian a distintas patologías, es prioritario (449).

En primer lugar, la nutrición adecuada se considera preventiva frente a enfermedades y complicaciones patológicas. Por una parte, se hablará del estado nutricional, que se encuentra amenazado en las personas mayores durante enfermedades agudas o crónicas, y de manera especial, durante los ingresos hospitalarios. La desnutrición repercute negativamente en la calidad de vida de la persona y fomenta su dependencia y su vulnerabilidad.

Se sabe también de la importancia de la realización del ejercicio físico y se recomienda mantener una actividad física regular. De los datos ofrecidos por la encuesta europea de salud para España (450) del año 2020, existe un porcentaje bajo de personas que realizan

ejercicio físico regularmente: 31.4% del sexo masculino y 21.9% del femenino. Es un dato alarmante que un casi 37% de la población total española se declare sedentaria, este porcentaje aumenta en el grupo de edad de entre 75 y 84 años (50%) y este porcentaje llega al 75% entre los mayores de 85 años.

En cuanto a hábitos tóxicos (450), sigue disminuyendo el porcentaje y tan sólo el 8.7% de la población mayor de 65 años se considera fumador habitual. Tampoco supone un problema el consumo de alcohol en España, ya que un 38,5% de las personas de entre 65 y 74 años y las personas mayores de 75 años no consume nunca alcohol Las diferencias son notables entre sexos, ya que los hombres beben más alcohol que las mujeres en los grupos poblacionales entre 65 y 74 años (449).

ANTECEDENTES Y ESTADO ACTUAL DEL TEMA

I. Diagnóstico de la EA

Para el diagnóstico neurológico de las demencias, se debe obtener una historia clínica detallada del usuario, un examen neurológico completo con una buena exploración física y exploración neuropsicológica (451). Para la historia clínica se deben recoger los antecedentes del individuo, la historia educativa, la historia médica, los fármacos que toma, la exposición a tóxicos… De esta manera se reunirá información del usuario que permitirá conocer el perfil evolutivo de la enfermedad.

La evaluación neuropsicológica se constituye de métodos y técnicas que muestran las capacidades mentales de los pacientes. Se pueden realizar test que evalúan de forma global las funciones cognitivas, aunque otros se centran más en la valoración de actividades de la vida diaria, la calidad de vida u otros ámbitos neuropsicológicos (452). Entre estos tres, se pueden incluir la exploración neuropsicológica de Barcelona, el mini mental State Examination (MMSE) o el Miniexamen cognoscitivo (MEC). Este último fue validado en

España y es el test abreviado de mayor validez y difusión internacional; resulta muy efectivo para el rastreo inicial de alteraciones cognitivas (453).

Las pruebas de neuroimagen donde se encuentra la tomografía computarizada (TC) o la resonancia magnética (RM), permiten excluir causas secundarias de demencia como tumores, hidrocefalia o infartos cerebrales…(452) En la tomografía computarizada se puede apreciar la atrofia progresiva de las diferentes áreas cerebrales y observar su evolución tras iniciar el tratamiento.

Los criterios del DSM-V (198) propuestos por la APA en el año 2014, los de la CIE-11 (454) formulados por la OMS en el año 2019 y los del National Institute of Neurologic Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) (228) intentan delimitar o concretar las características clínicas que han de tener las demencias (443). No obstante, estas clasificaciones no aúnan todos los síntomas clínicos que contempla esta enfermedad. Continuamente, se proponen revisiones de estos criterios tanto para la EA como para las demencias vasculares y frontotemporales.

Según la undécima edición de la CIE 11 (455), la última publicada, la demencia es un síndrome debido a una enfermedad cerebral, de naturaleza crónica o progresiva, con déficits de múltiples funciones superiores (memoria, pensamiento, orientación, comprensión, cálculo, capacidad de aprendizaje, lenguaje juicio, entre otras) y conciencia clara. En esta clasificación, el déficit se acompaña de deterioro del control emocional, del comportamiento social o de la motivación, produciendo un deterioro intelectual apreciable que repercute en las actividades de la vida diaria, con una duración del cuadro no inferior a seis meses y habiéndose obtenido la información de la exploración del paciente y de la anamnesis a una tercera persona (456).

El manual diagnóstico y estadístico de las enfermedades mentales (DSM-V) de la asociación americana de psiquiatría (APA) en su quinta edición (198), ha modificado sustancialmente sus criterios con respecto a la versión anterior. En esta versión se contempla un estadio patológico pre-demencia y se ha introducido el concepto de "trastornos neurocognitivos". Así, estos trastornos se dividen en tres categorías donde la sintomatología estudiada para el diagnóstico será: atención, función ejecutiva, aprendizaje, memoria, lenguaje, funciones viso perceptivas y visuales constructivas y cognición social. Las categorías divididas son: delirium, trastorno neurocognitivo mayor y trastorno neurocognitivo menor, estos últimos se diferencian por la intensidad de los síntomas y su repercusión en la funcionalidad del paciente (457). En estas categorías, por tanto, quedaría incluido el diagnóstico de EA con el nombre trastorno neurocognitivo debido a EA.

El National Institute of Neurologic Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA)(228), estableció los criterios diagnósticos para la EA en el año 1984, en los primeros criterios, se cometieron muchos errores ya que, entre otras cosas, no se había descrito todavía la demencia por cuerpos de Lewy y se desconocía el concepto de deterioro cognitivo leve sin demencia. Tras el paso del tiempo y del avance en los conocimientos de la enfermedad, se establecieron finalmente dos estadios en la enfermedad Alzheimer: un primer estadio preclínico, asintomático y un segundo estadio sintomático, que abarcaba desde que aparecieron las primeras quejas cognitivas hasta las fases más avanzadas de la demencia (456).

En los últimos años se han publicado dos conjuntos de criterios que establecen nuevos criterios de diagnóstico en la demencia y la EA. Por una parte están los criterios de Dubois et al. y por otra parte, la actualización de los criterios NINCDS-ADRDA, que fueron revisados en el año 2011 y constituyen ahora los nuevos NIA-AA (456).

Estos criterios, proponen la siguiente terminología para clasificar a usuarios con demencia causada por EA, de esta manera se distingue entre: probable demencia por EA, posible demencia por EA y posible demencia por EA con evidencia del proceso fisiopatológico de la EA (458).

Aunque se han realizado numerosas investigaciones acerca de la EA, todavía no se ha encontrado la causa que origina todas las lesiones mencionadas (459). Tras muchos estudios, parece claro que no se trata de una única causa, sino que el inicio de la EA es una combinación de diversos factores que desencadenan los cambios cerebrales y neuronales que se producen (460).

En la actualidad, los estudios acerca de la EA continúan efectuándose. Aún no se ha determinado la causa que origina esta enfermedad, aunque se siguen postulando hipótesis para explicar las lesiones neurodegenerativas características de esta patología (461).

II. Tratamiento y prevención de la EA

Actualmente, existen diferentes recursos terapéuticos, farmacológicos y no farmacológicos cuyo objetivo consiste en ralentizar el desarrollo de la enfermedad, mitigar la gravedad de los síntomas y mejorar la calidad de vida de los enfermos y de sus cuidadores (462). Todavía no se dispone de un tratamiento definitivo que sea capaz de detener el curso de la EA, los diferentes tratamientos están encaminados a ralentizar el curso de la enfermedad, de esta manera se siguen desarrollando investigaciones en este campo para conocer aspectos de la enfermedad que todavía no han sido descubiertos y que en un futuro lograrán determinar cómo abordar la enfermedad.

El tratamiento farmacológico persigue dos objetivos, el primero de ellos ralentizar el avance de la enfermedad y de esta manera, mantener y/o mejorar el rendimiento cognitivo de los enfermos; y por otra parte controlar los trastornos y alteraciones de conducta que aparecen en el curso de la enfermedad (463).

Primeramente, se abordará el tratamiento farmacológico de la sintomatología cognitiva, donde son numerosos los ensayos farmacológicos que se han realizado hasta la fecha. En este caso se administra tetrahidroaminoacridina en el cerebro de pacientes que sufren la EA, esta familia de fármacos actúa sobre el sistema colinérgico (464). El objetivo de este tratamiento se basa en aumentar los niveles cerebrales del neurotransmisor de la acetilcolina. Los fármacos que se emplean dentro de esta familia y que realizan esta función son la tacrina (mejora el rendimiento intelectual global en demencia leve o moderada), donecepilo (se recomienda en demencia leve y moderada, su empleo estabiliza el curso de la patología y puede llegar a mejorar las manifestaciones sintomatología), rivastagmina (retrasa su avance en tratamientos prolongados) y galantamina (se aplica desde los estadios iniciales de la patología y facilita un enlentecimiento considerable en etapas leves y moderadas) (465).

La segunda parte del tratamiento farmacológico no es otra que abordar la complejidad de la sintomatología psiquiátrica. Entre estas manifestaciones psiquiátricas pueden aparecer delirios, alucinaciones, depresión, alteraciones del sueño y modificaciones de la personalidad que pueden acarrear agitación, agresividad o desinhibición sexual (464). Para el tratamiento de estas manifestaciones se recomienda el menor número de fármacos posibles, ya que parte de estos síntomas son tratables mediante la readaptación de los hábitos del usuario y mediante estrategias de afrontamiento de los cuidadores. Entre el tratamiento farmacológico para tratar esta sintomatología se encuentran: los antipsicóticos: que se utilizan para tratar la agitación, agresividad y las conductas psicóticas y los más utilizados son los de última generación; los neurolépticos atípicos, que tienen menos efectos secundarios; las benzodiazepinas, para el tratamiento de la ansiedad, aunque por sus efectos secundarios en la actualidad es más recomendable el uso de fármacos como la trazodona. En ocasiones también se utilizan fármacos antidepresivos, los más indicados por su alta efectividad y su bajo rango de síntomas secundarios son los inhibidores selectivos de la recaptación de serotonina. Para el tratamiento de la agitación, se utilizan antiepilépticos (465).

Si se habla de prevención, lo primero que hay que dejar claro es que sólo entre el 1% y el 3% de los casos se debe a un patrón hereditario de herencia autosómica dominante (443). En estos usuarios hay mutaciones genéticas que causan la enfermedad. Estas mutaciones genéticas junto con otros genes actualmente desconocidos, además de factores ambientales y personales incrementan el riesgo de sufrir y padecer la EA. Un 33% de los casos de EA se atribuyen a factores de riesgo potencialmente modificables, con lo que se podría afirmar que podría prevenirse con una intervención multifactorial (466).

Para disminuir la incidencia de demencias y prevenir su posible aparición prematura se debe adoptar un estilo de vida saludable, realizando ejercicio físico e intelectual diario y manteniendo una dieta saludable y equilibrada (443). La actividad física habitual y mantenida durante años se asocia a una menor probabilidad de demencia, también ayuda a reducir el colesterol y la presión arterial y mejora la calidad del sueño. Se recomienda ejercicio aeróbico moderado como andar, correr, nadar o montar en bicicleta, según las posibilidades y limitaciones de cada uno. En cuanto a la alimentación es recomendable la dieta mediterránea. Esta dieta consiste en comer de todo y aumentar el consumo de frutas y verduras. También conviene consumir las legumbres y los frutos secos. Un estudio reciente pone de manifiesto que tanto la dieta específica para reducir la tensión arterial como la dieta mediterránea se asocian a tasas más lentas de deterioro cognitivo (467). La actividad intelectual contribuye a mejorar la reserva cognitiva que se asocia con una mayor resistencia del sujeto al daño cerebral ya que éste tenga una menor funcionalidad cognitiva, es decir, se comporta como un factor protector de demencia (443). Se puede mejorar la reserva cognitiva leyendo libros, escribiendo, con juegos de mesa o incluso, con actividades de nuevas tecnologías.

En cuanto a la prevención secundaria, hasta el momento no existen vio marcadores para el diagnóstico de la EA. En resumen, la prevención actual de la EA se basa en el control de los factores de riesgo, de esta manera se podrían evitar el 30% de los casos (443). Estas

medidas consisten en proporción a la persona un envejecimiento saludable, y para ello, es aconsejable llevar una dieta equilibrada y saludable y realizar a diario ejercicio físico e intelectual.

METODOLOGÍA

I. Objetivo

Aplicar modelos de regresión lineal a la diagnosis de enfermedades en personas mayores, a partir de matrices de datos con muchas variables y casos. Esta metodología debe ser capaz de generar modelos de diagnosis robustos y con buena fiabilidad

II. Población de estudio

Se trata del tipo de muestreo de conveniencia, técnica no probabilística, donde las personas que participaron en el estudio se seleccionaron por la disponibilidad para participar en el mismo.

La muestra está conformada por 508 hombres y 947 mujeres. Un total de 1455 usuarios. La recogida de la muestra se produjo entre las fechas Octubre del 2008 y octubre de 2020 en una residencia de personas mayores de la capital de Burgos.

En cuanto a la edad media del total de la muestra es 85.48 años, para hombres es inferior, situándose en 83.69 y para la mujer es superior a la media, con un valor de 86.44. Los mínimos de edad de participación en el estudio son de 60 (Total de la muestra y hombres) y 62 años para mujeres. Los valores máximos de edad son de 106 años (Total de la muestra y mujeres) y 105 años para los hombres. Los datos en formato de figuras y tablas están recogidos en el anexo 6: Tablas A6-A9; Figuras A1-A8.

- Estadísticos descriptivos de la muestra: signos vitales y de medición corporal

Los signos vitales indican el estado funcional de los usuarios, y se consideran herramientas valiosas para determinar problemas en el organismo, ya que una alteración en cualquiera de ellos supone una patología de base. Los datos en formato de figuras y tablas están recogidos en el anexo 6: Tablas A10-A18.

Es la onda pulsátil de la sangre, originada en la contracción del ventrículo izquierdo del corazón y que resulta en la expansión y contracción regular del calibre de las arterias. La onda pulsátil representa el rendimiento del latido cardiaco, que es la cantidad de sangre que entra en las arterias con cada contracción ventricular y la adaptación de las arterias, o sea, su capacidad de contraerse y dilatarse (468).

El pulso periférico se palpa fácilmente en pies, manos, cara y cuello. Realmente puede palparse en cualquier zona donde una arteria superficial pueda ser fácilmente comprimida contra una superficie ósea (468).

La velocidad del pulso (latidos por minuto) corresponde a la frecuencia cardiaca, la cual varía con la edad, sexo, actividad física, estado emocional, fiebre, medicamentos y hemorragias (468).

Los valores normales para la constante vital de frecuencia cardíaca son: recién nacidos (Entre 120-170 pulsaciones por minuto); niños de 2 a 4 años entre 100 y 120; los niños de 6 a 8 años entre 100 y 115 pulsaciones por minuto y en personas adultas oscilan entre 60 y 80. En el anexo 6 se pueden ver los valores descriptivos recogidos en la muestra con referencia a la frecuencia cardíaca.

El control glucémico de los pacientes diabéticos deberá estar encaminado a tener glucemias de ayuno < 120 mg/dl (< 6.6 mmol/L) y hemoglobina glucosilada < 7%11-14 (469).

La tensión arterial consiste en la presión que ejerce la sangre sobre las paredes arteriales cuando circula por las arterias en el organismo. Como la sangre se mueve por ondas, se pueden dar dos tipos de medidas de tensión o presión arterial: la tensión sistólica, que es la presión de la sangre debida a la contracción de los ventrículos, es decir, la presión máxima; y la tensión diastólica, que es la presión que queda cuando los ventrículos se relajan; ésta es la presión mínima (235,470).

- Estadísticos descriptivos de la muestra: medicamentos

La clasificación Anatómica Terapéutica Química (ATC) consiste en un sistema europeo de codificación de sustancias farmacéuticas y medicamentos en cinco niveles con arreglo al sistema u órgano efecto y al efecto farmacológico, las indicaciones terapéuticas y la estructura química de un fármaco (471). De esta manera a cada medicamento le corresponde un código ATC, y a su vez este código se especifica en una ficha técnica (donde aparecen resumidas las características del producto) del medicamento (472).

La clasificación ATC se estructura en cinco niveles (471):

- 1.er nivel (anatómico): órgano o sistema sobre el que actúa el fármaco (existen 14 grupos en total).
- 2.o nivel: subgrupo terapéutico.
- 3.er nivel: subgrupo terapéutico o farmacológico.
- 4.o nivel: subgrupo terapéutico, farmacológico o químico.
- 5.o nivel: nombre del principio activo (mono fármaco) o de la asociación medicamentosa

En la clasificación cada nivel o categoría se distingue mediante una letra y un número o una serie de letras y números. En este sistema de clasificación, todos los preparados a base de un mismo y único fármaco reciben un código idéntico (471).

Los medicamentos que se recogen en la muestra están divididos conforme al tercer nivel, de manera que se han creado subgrupos farmacológicos de clasificación de los distintos medicamentos atendiendo al tercer nivel de la codificación farmacológica ATC.

La clasificación en España se reguló a partir del Real decreto 1348/2003, del 31 de octubre (473), por el que se adaptó la clasificación anatómica de medicamentos al sistema de clasificación ATC, en el plazo de tres años desde su entrada en vigor, se regulaba que España adaptaría la clasificación de medicamentos a la clasificación de la Unión Europea denominada ATC. Los datos descriptivos están recogidos en el anexo 6: Tabla A23.

- Estadísticos descriptivos de la muestra: patologías

La Clasificación Estadística Internacional de Enfermedades y Problemas Relacionados con la Salud (CIE-11) es la Undécima Revisión de la Clasificación Internacional de Enfermedades (CIE) que desde 1948 está a cargo de la Organización Mundial de la Salud (OMS) (446). Se ha utilizado la clasificación CIE 11 para clasificar las distintas patologías identificadas en la muestra total. Del total de 1117 patologías, se muestran en el anexo 6: tabla A24, donde las patologías se clasifican en 41 grupos atendiendo a la clasificación internacional (CIE-11).

La CIE es una clasificación realizada por la agencia internacional de las Naciones Unidas, un recurso público de libre acceso para servir de herramienta en la salud pública (455). CIE-11 es una clasificación orientada a describir morbilidad y causas de muerte. Con sus más de 14.000 códigos es posible codificar la mayoría de los diagnósticos más frecuentes tanto en ámbitos ambulatorios como de internación (454).

III. Criterios de inclusión y exclusión

En cuanto a los criterios de inclusión que conforman el estudio se presentan a continuación:

- Edad comprendida entre 65- 85 años.

- Haber tenido al menos una valoración cognitiva con una herramienta estandarizada (Pfeiffer, MEC o LOTCA-G)
- Diagnóstico clínico de la EA probable según los criterios NINCDS-ADRDA (1984) o DSM valorado en la Unidad de Diagnóstico
- Usuario de residencia con al menos una permanencia de 3 meses.

En cuanto a los criterios de exclusión que conforman el estudio se presentan a continuación:

- Pacientes con problemas conductuales graves: delirium, alucinaciones.
- Pacientes sometidos a otro cualquier tipo de tratamiento psicosocial.

IV. Instrumentos de valoración

Para la recogida de datos se han utilizado los registros almacenados durante 10 años de manera digital en una residencia de ancianos.

Tabla 28. Variables independientes de la muestra

Variables independientes	
Variables sociodemográficas	Variables clínicas
Edad	Frecuencia cardíaca
Sexo	Peso
Estado Civil	Índice de Masa Corporal
Tipología de plaza	Glucemia
	Presión arterial sistólica
	Presión arterial diastólica
	Medicamentos
	Patologías
	Bebedor
	Fumador

Las variables recogidas fueron las siguientes:

La variable dependiente o de resultado consiste en el registro de los residentes diagnosticados de EA en la base de datos de origen.

En cuanto a las variables independientes o factores de estudio se incluyen:

V. Procedimiento de recogida de datos

El trabajo de campo (recogida de datos) consistió en la recogida de información en los registros historiales de los usuarios de la residencia. Una vez recogida toda la información se confeccionó la base de datos y se realizó la implementación del análisis estadístico de los datos de la matriz de datos original con el fin de aplicar todas las técnicas mencionadas. Se compararon los resultados obtenidos en la síntesis de meta-análisis con los de este estudio.

VI. Consideraciones éticas

Según Rueda (474) en su estudio, esta tesis se podría considerar como una investigación a través de sujetos humanos, donde el interés está centrado en la dinámica social, los efectos socioeconómicos y en los intereses comunitarios. Los proyectos diseñados como formas de investigaciones sociales usan a las personas como "informantes". No hay beneficios personales acumulados por la investigación, tampoco los productos son las metas, sí los principios y estructuras sociales hacia donde se dirigen (475).

Según el National Research Council of the National Academies (476), la integridad de la investigación puede definirse como una serie de buenas prácticas que incluyen (477), entre otras la protección de las personas que intervienen en las investigaciones o el cumplimiento de las responsabilidades mutuas entre los investigadores y los participantes de una investigación.

Se ha tenido en cuenta la normativa de España con referencia a la protección de datos, regulada por la ley LOPD o Ley Orgánica de protección de datos (478) en la que se regula

la obligación que tiene toda persona que interviene en cualquier fase del tratamiento de datos personales, de garantizar la seguridad de dichos datos, y evitar así la apertura de inspecciones por parte de la Agencia Española de Protección de Datos y en su caso de los correspondientes procedimientos sancionadores.

En la declaración de Helsinki (479) del año 1964, revisada en el año 2013 fue elaborada por la asociación médica mundial (AMM) para la investigación médica en seres humanos, incluyendo la investigación del material humano y de información identificables. En los principios generales de la declaración se concluye como objetivo principal de la investigación en seres humanos comprender las causas, evolución y efectos de las enfermedades y mejorar las intervenciones preventivas, diagnósticas y terapéuticas. El objetivo general de la investigación médica es generar nuevos conocimientos, aunque este objetivo no debe tener nunca primacía sobre los derechos y los intereses de las personas que participan en la investigación. Además, se deben considerar las normas y estándares éticos, legales o jurídicos para la investigación en seres humanos en el propio país, al igual que las normas y estándares internacionales vigentes. Todos los datos tomados, han sido tratados con la máxima precaución para resguardar la intimidad de la persona que participa en la investigación y la confidencialidad de su información personal.

Como se estipula en la declaración de Helsinki, esta tesis ha pasado por un comité de investigación, el Comité de ética de investigación de la Universidad de Burgos, donde se han considerado las leyes y reglamentos vigentes en España donde se realizó la investigación, pero también las normas internacionales vigentes. La Comisión de bioética de la Universidad de Burgos en cumplimiento de lo previsto en los Estatutos de la Universidad de Burgos, el Consejo de Gobierno, con fecha del 6 de noviembre de 2008, aprobó la creación de la Comisión de Bioética, consciente de la significación actual de esta temática y de su responsabilidad como institución con vocación de servicio público en interés social (480).

En la investigación también se han tenido en cuenta los principios éticos básicos del informe de Belmont (481) del año 1979. Estos principios representan los preceptos éticos y las valoraciones particulares de las acciones humanas. Son tres: respeto a las personas, beneficencia y justicia:

También se han seguido las pautas éticas internacionales para la investigación biomédica en seres humanos preparadas por el Consejo de organizaciones internacionales de las ciencias médicas (CIOMS) en colaboración con la organización mundial de la salud a en Ginebra en el año 2002. Se redactan las que conciernen a la investigación (477).

Por último, también se ha tenido en cuenta el código ético de Terapia Ocupacional (474), elaborado por la asociación americana de Terapia Ocupacional, que consiste en una declaración de valores y principios que promueven y mantienen unas normas de comportamiento en la práctica de la profesión de Terapia Ocupacional. El código ético de terapia ocupacional supone unos principios que se aplican en todos los ámbitos de la profesión, incluido el investigador (474).

Se tendrá en cuenta la normativa de España con referencia a la protección de datos, regulada por la ley LOPD o Ley Orgánica de protección de datos (478) en la que se regula la obligación que tiene toda persona que interviene en cualquier fase del tratamiento de datos personales, de garantizar la seguridad de dichos datos, y evitar así la apertura de inspecciones por parte de la Agencia Española de Protección de Datos.

RESULTADOS

El objetivo de este trabajo ha sido aplicar modelos a la diagnosis de enfermedades en personas mayores, a partir de matrices de datos con muchas variables y casos. De esta manera se ha aplicado el método desarrollado en la primera parte de esta segunda sección usando los tres clasificadores lineales: ADL, RL y SVM.

I. Resultados de predicción de los clasificadores

Se aplicaron los clasificadores de ADL, RL y SVM al método diseñado en la primera parte con la muestra de los sujetos que tienen EA, y se seleccionaron un total de 46 variables que se consideraron pertinentes para el modelo después de revisar la literatura científica en base a los factores de riesgo que pueden predecir la EA.

Como se muestra en la tabla 29, para una sola variable todos los clasificadores reflejan un 74.87% de precisión en la clasificación. Lograr una precisión superior al 74% para cada clasificador, se interpreta como un resultado valioso. Con dos variables RL predice mejor con un 79.58% y sigue en esa misma línea si se aumentan las variables, hasta que llega a predecir un 83.20% con 10 variables. ADL con el mismo número de variables (10), predice un 81.07% y SVM un 83.07%.

Tabla 29. Resultados de predicción de los clasificadores

NºV	ADL	NºV	RL	NºV	SVM
1	0,748708	1	0,748708	1	0,748708
2	0,749354	2	0,795866	2	0,77261
3	0,763566	3	0,807494	3	0,79522
4	0,781654	4	0,817829	4	0,81137
5	0,80168	5	0,823643	5	0,822351
7	0,805556	6	0,826227	6	0,824935
8	0,810078	7	0,828165	7	0,828165
10	0,810724	8	0,830103	8	0,829457
		9	0,831395	9	0,830103
		10	0,832041	11	0,830749
				15	0,831395
				18	0,832687
				19	0,833333

Este último clasificador predice hasta con 19 variables, llegando al 83.3% de predicción, solo un 2% más que ADL y con un aumento de 9 variables más, por lo que resulta más complejo y menos pragmático en el diagnóstico de EA. Por lo tanto, como se puede ver en la figura 32, RL predice mejor, con menor número de variables y mayor predicción.

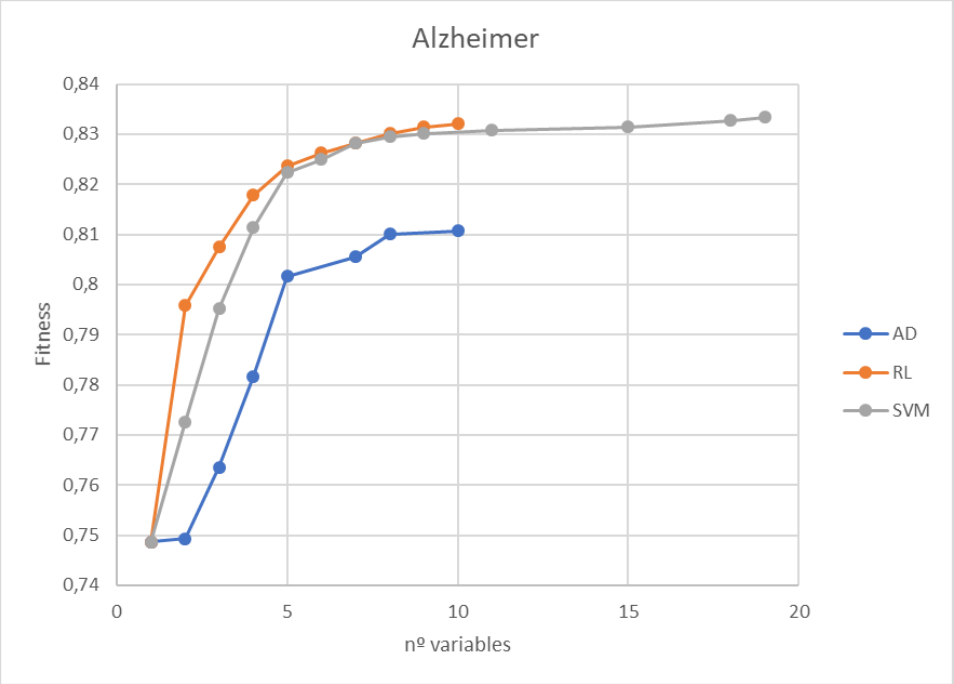

Figura 32. Gráfica comparativa entre el número de variables y el fitness de los clasificadores

II. Elección de modelo entre los distintos clasificadores

- Análisis de los modelos obtenidos con ADL

Basándonos en el conjunto de variables extraídas de la base datos, el método clasificó a los pacientes en sanos o con EA mediante el clasificador de ADL. La precisión de clasificación comenzó en un 74.87% con una variable, y alcanzó un 81% con 10 variables. Como se observa en la tabla 30, ADL indica que haber padecido un ictus predice un 74.87% en la probabilidad de desarrollar EA. Aumenta un 0.6% la probabilidad si se añade la variable edad en la ecuación. Si se combinan las variables no tomar medicamentos antiarrítmicos, ser

fumador y haber tenido un ictus, la probabilidad aumenta un 1.48% con respecto al modelo de una única variable.

Tabla 30. Modelos de clasificación con el clasificador ADL

Acuraccy	Variable	Coeficiente
0,748708	Ictus	-0,750361
0,749354	Edad	0,506483
	Ictus	-0,014654
0,763566	Antiarrítmicos	-0,02833
	Fumador	-1,354246
	Ictus	0,689096
0,781654	Antipsicóticos	0,014948
	Fumador	-1,126289
	Enfermedades del corazón	0,741464
	Ictus	-0,378047
0,80168	Antiarrítmicos	-0,127157
	Betabloqueantes	-1,321392
	Fumador	0,34964
	Bebedor	0,684717
	Ictus	0,343325

Con 4 variables el modelo llega a predecir un 78.16%, alcanzando su mejor predicción con el menor número de variables con 5 variables: no tomar medicamentos antiarrítmicos y betabloqueantes, ser fumador y bebedor y haber padecido un ictus, el modelo predice un 80.16% la EA.

Así pues, en ADL se repite en cada modelo la variable ictus, determinando que se trata de una patología relacionada directamente con la EA en este caso. También cobra un papel

importante la variable fumador, presente en 3 modelos de los 5 presentados. No tomar antiarrítmicos, también está presente en 2 modelos en ADL.

- Análisis de los modelos obtenidos con RL

Se ha aplicado el algoritmo creado y se ha usado el clasificador del modelo de regresión lineal, la variable final, entonces, fue la EA. Este modelo determinará si un paciente tiene o no, la probabilidad de desarrollar Alzheimer.

Como se observa en la tabla 31, la variable ictus predice un 74.87% la probabilidad de desarrollar EA. En el modelo de 2 variables, no tomar medicamentos antiarrítmicos y padecer un ictus predicen un 4.71% más. Si se cambian las variables por ser fumador, bebedor y haber padecido un ictus, la probabilidad de desarrollar EA es un 80.74%. Con las 4 variables mostradas en la tabla 31, tomar betabloqueantes, ser fumador y padecer enfermedades del corazón y haber tenido un ictus, la probabilidad con respecto al modelo anterior aumenta un 1%. En el modelo 5 de RL, la combinación de estas las 5 variables mostradas, predice un 82.36%. Entendiendo este modelo como un buen modelo con alto nivel de acierto con el menor número de variables.

Los resultados se muestran en la tabla 31. La variable ictus aparece en todas las combinaciones. Las variables "fumador", "antiarrítmicos", "betabloqueantes" y "enfermedades del corazón" aparecen en 2 de los modelos, por lo que cobran también especial importancia dentro del método. La variable "bebedor" solo se muestra en uno de los modelos.

Tabla 31. Modelos de clasificación con el clasificador ADL

Probabilidad	Enfermedad	Coeficiente
0,748708	Ictus	2.039428
0,795866	Antiarrítmicos	-0.014654
	Ictus	2.020273
0,807494	Fumador	-1.354246
	Bebedor	0.689096
	Ictus	1.469136
0,817829	Betabloqueantes	-1.126289
	Fumador	0.741464
	Enfermedades del corazón	0.378047
	Ictus	1.625869
0,823643	Antiarrítmicos	-1.321392
	Betabloqueantes	0.349640
	Fumador	0.684717
	Enfermedades del corazón	0.343325
	Ictus	1.438381

- Análisis de los modelos obtenidos con resultados SVM

Se pretende utilizar para terminar un clasificador basado en un híper plano que sea más robusto y tenga mayor capacidad predictiva al aplicarlo a nuevas observaciones. SVM es un método de clasificación simple, intuitivo y eficiente utilizado por investigadores y científicos para la clasificación de datos. Este clasificador toma la decisión de comparar una muestra recién etiquetada (datos de prueba) con los datos de referencia (datos de entrenamiento). Según este enfoque y clasificador, un paciente se etiqueta como normal o infectado con EA según el resultado de la clasificación.

De esta manera como se muestra en la tabla 32, se han obtenido los siguientes modelos. Como en los clasificadores anteriores, la variable ictus parece la más determinante por sí misma y también en combinación con el resto de los modelos, ya que se presenta en la mayoría. Del mismo modo, tener la tensión alta y no tomar antiarrítmicos, aparecen en todos los modelos excepto el primero. Otras variables como ser fumador, tomar betabloqueantes o tomar antidiabéticos, se presentan en algunos modelos de manera esporádica.

Tabla 32. Modelos de clasificación con el clasificador SVM

Probabilidad	Variables	Coeficiente
0,748708	Ictus	1,991592
0,77261	Antiarrítmicos	-0,992188
	Hipertensión arterial	1,993283
0,79522	Antiarrítmicos	-1,005837
	Hipertensión arterial	0,998879
	Ictus	1,009364
0,81137	Antiarrítmicos	-1,003555
	Fumador	-0,994749
	Hipertensión arterial	0,984955
	Ictus	1,006583
0,822351	Antidiabéticos	-0,987738
	Antiarrítmicos	-0,012114
	Betabloqueantes	-1,005521
	Hipertensión arterial	0,003837
	Ictus	0,99922

Este clasificador difiere en algunas variables con los otros dos mostrados. Como se puede observar en la tabla 32, en el primer modelo, la variable que predice EA es ictus con una probabilidad del 74.87%, al igual que en el resto de los clasificadores. Si se cambian las

variables por sufrir hipertensión arterial y no tomar antiarrítmicos, la probabilidad aumenta un 2.39%. En el tercer modelo, al juntar las 3 variables mencionadas anteriormente: sufrir un ictus, tener hipertensión arterial y no tomar antiarrítmicos, la probabilidad sigue aumentando en un 2.26%. En el cuarto modelo, si se añade a todas las variables anteriores ser fumador, se sigue aumentando la probabilidad, en este caso un 1.61%. Y, por último, en el modelo con 5 variables en el que se presenta no tomar antiarrítmicos, ni antidiabéticos y betabloqueantes, haber sufrido un ictus y tener hipertensión arterial, mejoraría en la ratio de aciertos con un 82.23%.

DISCUSIÓN

Se puede observar que hay ciertas variables que tienen una mayor probabilidad en el desarrollo del Alzheimer. El objetivo de este estudio fue evaluar la asociación de distintos factores de riesgo con la probabilidad de desarrollar EA.

I. Variables presentes en todos los clasificadores (ADL, RL y SVM)

La contribución del ictus al riesgo de EA de inicio tardío se ha debatido durante mucho tiempo. En nuestro estudio, la variable ictus aparece en los 3 clasificadores y en casi todos los modelos de cada uno de ellos. La ciencia indica que las enfermedades cardíacas y los ictus son dos de las principales causas de muerte y discapacidad en el mundo (482). La evidencia científica muestra una fuerte asociación entre distintos factores de riesgo, incluyendo el ictus. En el meta-análisis realizado por Zhou et al. (483) se concluyó que el ictus aumentó de manera significativa e independiente el riesgo de EA y, a su vez, la EA aumentó el riesgo de ictus. En el estudio de cohorte presentado por Chi et al. (344) también se concluye que el diagnóstico clínico de la EA se asocia con un riesgo considerablemente mayor de desarrollar un accidente cerebrovascular. Por lo tanto, se observa en la literatura que nuestros resultados aparecen relacionados directamente con otros hallazgos y concuerdan de la misma manera.

En general, la literatura indica que el tabaquismo antiguo/activo está relacionado con un riesgo significativamente mayor de EA (50,484,485). Los resultados de esta investigación también apoyan la relación de la variable ser fumador, que está relacionada con alguno de los modelos presentados en los 3 clasificadores. Algunas de las teorías que vinculan esta variable como factor de riesgo de la EA se relacionan con la vinculación de fumar como factor de riesgo de enfermedades vasculares, que influyen directamente en la patogenia de la EA (486,487). En esa misma línea el abandono sostenido del hábito de fumar se asocia con una disminución significativa del riesgo de enfermedades cardiovasculares, enfermedades pulmonares obstructivas crónicas y de EA (488). Otros artículos concluyen que no existe una asociación entre el tabaquismo y el riesgo de EA (489), algunos lo atribuyen a la interacción del genotipo APOE€4 en la etiología de la EA(489), otros concluyen que fumar no afecta al rendimiento cognitivo en personas mayores de 75 años (490).

Otra de las variables directamente relacionada con la probabilidad de desarrollar EA y que en los resultados se presenta en todos los clasificadores (ADL, RL y SVM), es la toma de medicamentos antiarrítmicos como factor protector de la EA. Los efectos del tratamiento con antiarrítmicos sobre la cognición y los marcadores relacionados con la EA se han estudiado en diferentes estudios (491,492), pero la literatura hasta el momento no es muy extensa de la relación existente entre estas dos variables. Aunque a pesar de la escasa información al respecto, los estudios encontrados concluyen que el propranolol (uno de los principales medicamentos que se utilizan como anti arrítmico), refuerzan su potencial como agente terapéutico para la EA (491,493).

En la misma línea que la variable anterior, la toma de medicamentos betabloqueantes, también disminuye la probabilidad de sufrir EA, y así se manifiesta en los resultados presentados, donde esta variable aumenta la ratio de aciertos en todos los clasificadores

presentados. Se sugiere por tanto que la toma de este tipo de medicamentos en personas de edad avanzada está implicada como protector en el desarrollo de la EA. Pero esto es contrario al estudio reciente realizado por Holm et al. (494) donde se observó que el uso de betabloqueantes se asociaba con un riesgo dos veces mayor de EA posterior en la población general de edad avanzada. Esta interacción puede deberse a que los medicamentos betabloqueantes poseen importantes capacidades de regulación para las funciones cognitivas y conductuales (495). También se ha argumentado que el mecanismo detrás del deterioro cognitivo inducido por betabloqueantes es causado por una producción reducida de melatonina (496), en esa línea una reducción en los niveles de melatonina se correlaciona con la EA y se ha demostrado que la suplementación con melatonina retrasa la progresión de los pacientes con deterioro cognitivo leve a la EA(497). Pero otros estudios demuestran beneficios por la toma de betabloqueantes, por ejemplo, el uso de betabloqueantes después de un infarto de miocardio se ha asociado con una mayor disminución funcional en los residentes de hogares de ancianos (498). Otros muchos estudios demuestran la mejora de la insuficiencia cardíaca tras la toma de medicamentos betabloqueantes como el metoprolol (499), enalapril (500) o valsartan (501).

II. Variables presentes solo en dos de los clasificadores (ADL y RL)

ADL y RL comparten algunas de las variables que predicen la EA. La primera de ellas es "bebedor". El impacto del alcohol en la EA ha sido ampliamente estudiado, actualmente, existe discrepancia con respecto al impacto del alcohol sobre la EA (502). Los resultados de este estudio demuestran que ser bebedor aumenta la probabilidad de desarrolla EA en el futuro. En cuanto a la literatura, se contemplan dos teorías ampliamente respaldadas. Por una parte, el consumo de alcohol como factor protector frente a la EA. Algunos estudios respaldan que el consumo moderado/regular de alcohol tiene mayor efecto protector, entendiéndose como moderado: 0,25 a >1 bebida/día para mujeres; 0,25 a >2 bebidas/día

para hombres (503). Otros estudios analizan otras variables moderadoras en esa misma línea del alcohol como factor protector como sexo o raza, identificando el consumo de alcohol ligero a moderado como protector contra la EA en hombres (504) y el consumo regular de alcohol (>10 tragos/semana) como protector solo para afroamericanos (505). Por otra parte, otros estudios han concluido que el consumo de alcohol está asociado con un mayor riesgo de EA, en ese sentido el principal problema para determinar la relación es la medición de la cantidad de alcohol ingerida, que es muy variable: sí/no consume actualmente y/o consumió alguna vez, volumen consumido durante un período de tiempo específico (p. ej., litros/semana, gramos/día) y solo consumo excesivo de alcohol (>6 tragos por día durante 10 años) (502). Independientemente de los niveles variables de alcohol examinados en los estudios, los hallazgos con respecto a la asociación entre el alcohol y la EA no parecen ser muy concluyentes.

Los factores de riesgo cardiovascular están estrechamente relacionados con el riesgo de EA (506). La importancia de las complicaciones de las enfermedades cardiovasculares en la vejez se ha ampliado con los avances en la medicina cardiovascular en las últimas décadas. El cerebro es un órgano altamente vascularizado, recibe el 15 % del gasto cardíaco y representa alrededor del 20 % del consumo total de oxígeno del cuerpo (507). Esta razón podría explicar los resultados de este estudio donde se han asociado directamente las enfermedades cardiovasculares con la probabilidad de desarrollar EA. Otro de los motivos es que la EA se ha considerado una enfermedad específica del cerebro que se caracteriza por la presencia de placas y ovillos neurales de proteínas, que es lo que produce la sintomatología típica de la EA (508). Nuevas evidencias sugieren que las agregaciones de las proteínas mencionadas anteriormente, también se encuentran en las personas enfermedades cardiovasculares (508). En este sentido existen estudios que vinculan la EA con enfermedades cardiovasculares en distintas poblaciones (509,510). Los factores de riesgo cardiovascular como la cardiopatía

coronaria, la fibrilación auricular y la insuficiencia cardiaca se asocian con la demencia y el deterioro cognitivo (511).

III. Variables importantes en SVM

La hipertensión crónica se ha sugerido como uno de los mayores factores de riesgo modificables para desarrollar EA (208). En los resultados que se han mostrado con el clasificador SVM, la hipertensión aparece en todos los modelos, por lo que su importancia merece distinción. En esta línea existen muchos estudios que relacionan la hipertensión arterial con la EA. De hecho, uno de los capítulos de la primera sección de esta tesis, se encarga de analizar dicha relación. Los estudios epidemiológicos han demostrado que la hipertensión es un factor de riesgo para la demencia y la EA, pero la asociación es compleja. Por una parte, algunos estudios establecen una relación clara entre ambas variables, justificando esta relación en distintas teorías: la probabilidad de manifestar EA aumenta con la presencia de patología cerebrovascular (como se ha mencionado anteriormente), que está fuertemente ligada a la hipertensión (512,513). Además, la hipertensión no controlada parece que aumenta el nivel de ovillos neurofibrilares y placas neurales (que se ha señalado anteriormente como causantes directos de la EA), lo que provocaría una relación directa entre las dos variables (273,514). Otra de las teorías consiste en que algunos estudios también han observado una mayor atrofia cerebral con aumento de la presión arterial tanto en personas con demencia (515,516). Sin embargo, en el meta análisis realizado por Power et al.(517) no proporcionan pruebas claras de una relación entre la presión arterial y la EA, la justificación a estos resultados, podría explicarse por el papel de los medicamentos, si la presión arterial está causalmente relacionada con el riesgo de EA, el tratamiento de la hipertensión puede dificultar la detección de tal efecto en la población, y de esta manera no relacionar ambas variables.

IV. Variables comunes importantes en ADL y RL

Ambos clasificadores comparten varias variables en los distintos modelos. De esta manera, tomar antiarrítmicos, haber sufrido un ictus, haber sufrido enfermedades del corazón o ser fumador son comunes a ambos clasificadores y aparecen en la mayor parte de los modelos de manera combinada.

LA literatura avala estos resultados, estableciendo vínculos entre los factores vasculares y la EA (tanto a nivel clínico como patológico), pero la naturaleza de la relación aún no se ha establecido por completo y faltan estudios de tratamiento de alta calidad que examinen la medida en que la modificación del riesgo vascular altera la enfermedad de EA (518). Son muchas las teorías que avalan la relación existente entre estas variables, por ejemplo, por una parte, el daño cerebrovascular debido a factores de riesgo vascular y que desencadena directamente la demencia vascular (77). Por otra parte, cada vez es más evidente que los factores de riesgo vascular también aumentan el riesgo de EA neurodegenerativa, que se asocia con la acumulación de proteínas neurotóxicas en el cerebro (519).

La variable edad clasifica en ADL con un modelo de dos variables donde se incluye ictus y edad con un 74.93% de clasificación. La edad avanzada no causa la EA, pero es el factor de riesgo conocido más importante para la enfermedad (520). La cantidad de personas con la EA se duplica aproximadamente cada 5 años después de los 65 años (521). Aproximadamente un tercio de todas las personas mayores de 85 años pueden tener la EA (521).

La variable tomar betabloqueantes clasifica en RL en un modelo con 4 variables (Ser fumador, ictus, enfermedades del corazón y tomar betabloqueantes) donde la predicción aumenta hasta en un 6% con respecto al modelo de una única variable. La literatura avala estos datos, destacando el papel beneficioso de los betabloqueantes en la EA, que revierten

significativamente los déficits bioquímicos y de comportamiento inducidos por la enfermedad (522,523).

V. Variables presentes solo en algunos de los modelos

En los resultados, la edad, como se remarcaba anteriormente, también es una variable que se remarca como predictiva en el clasificador de ADL. En realidad, esto concuerda con la literatura científica. Hebert et al. (520) en el año 1995, ya concluían que la incidencia de la EA es aproximadamente 14 veces mayor entre las personas mayores de 85 años en comparación con las que tienen entre 65 y 69 años. En un estudio realizado en España, se concluye que la edad avanzada es el principal factor de riesgo de la EA, por lo que el envejecimiento de la población, debido a la mejora de la esperanza de vida, aumenta la incidencia y prevalencia de la EA, así como los costes económicos, sociales y emocionales asociados a esta enfermedad (208). Algunas de las razones por las que la edad puede influir en el desarrollo de la EA podrían ser varias. Por una parte y más allá del alelo ε4 de la apolipoproteína E (APOE), se sabe poco acerca de los genes asociados con y que aumentan el riesgo de EA (524). Un estudio realizado en 2019 de todo el genoma identificó un locus en el cromosoma 17 asociado con la edad de inicio de la EA (525). Además, las respuestas inflamatorias e inmunitarias tienen un papel importante en el desarrollo y progresión de la EA, y estas son más lentas y peores a medida que se aumenta la edad de la persona (379). Por otra parte, la edad y la EA ejercen patrones independientes de atrofia de la materia gris, pero estos efectos se superponen sustancialmente en el hipocampo y la corteza cerebral y conllevan a la progresión de la enfermedad (311). Sin embargo, otros estudios remarcan que algunos factores genéticos y no genéticos modifican el efecto de la EA en la edad y determinan la relación entre ambas variables (526,527).

En este estudio el uso de antipsicóticos se postula como una variable que influye en el diagnóstico de la EA. El uso de antipsicóticos en EA produce controversia en la literatura,

se ha analizado sobre todo el uso de estos fármacos en el tratamiento de los síntomas y la literatura es prácticamente inexistente para la relación que puede tener el consumo de antipsicóticos y el desarrollo de la EA. En esa línea se señala, que a pesar de todos los efectos adversos descritos y las recomendaciones de precaución en su uso, los antipsicóticos aún se utilizan ampliamente (528). La realidad es que este tipo de fármacos se prescriben de manera regular entre la población mayor y muchos facultativos alertan del peligro que supone usarlas de manera crónica(529). El uso de este tipo de fármacos, se vincula con otro tipo de enfermedades como la diabetes, en el estudio realizado por Chang et al. (530) se concluyó que el riesgo de diabetes fue elevado en pacientes con EA en tratamiento antipsicótico. Se debe tener en cuenta, como sucede en otras patologías, que las personas difieren en su respuesta a los medicamentos (531), se han usado los antipsicóticos para mejorar la sintomatología de la EA, y ha resultado ser eficaz (532), sin embargo para controlar las alteraciones del comportamiento que produce la EA, en otras ocasiones, se ha reducido el uso de antipsicóticos a largo plazo en pacientes diagnosticados de EA (533). Otra de las líneas que relaciona el uso de antipsicóticos con la EA es la psicosis, por ejemplo, en varios estudios las personas diagnosticadas de EA y que usaban medicamentos antipsicóticos, tenían más probabilidades de tener psicosis que los que no consumían esos fármacos (534,535). Los síntomas psicóticos son comunes y persistentes en pacientes con EA, aunque la investigación continua, en particular los estudios longitudinales, pueden revelar asociaciones biológicas y clínicas que informarán de la asociación futura entre estas variables (535).

Los factores de riesgo cardiovasculares y asociados al estilo de vida se reconocen cada vez más como importantes para la patogénesis de la EA. Los resultados que se presentan en este estudio indican que los fármacos antidiabéticos son protectores en la EA, ya que tomarlos disminuye el desarrollo de la EA. Estos resultados son acordes a la literatura científica, donde se ha concluido en otros estudios que los fármacos antidiabéticos pueden representar un

enfoque prometedor para combatir la EA (536). En este sentido, algunas patologías como la diabetes aumentan significativa e independientemente el riesgo de EA (38). La relación de la diabetes con la EA se puede explicar por diversas teorías. Los estudios han demostrado que una vía alterada de la insulina puede interactuar con el depósito de la proteína amiloide-β y la fosforilación de la proteína tau, ambos factores principales para el desarrollo de la EA (536). Además, la insulina actúa como factor de crecimiento en el cerebro y es neuro protectora, activa el brote dendrítico, la regeneración y la proliferación de células madre, por lo que el deterioro de esta importante señal del factor de crecimiento puede facilitar el desarrollo de la EA (537). Todas estas afirmaciones, pueden explicar los resultados obtenidos, si las teorías e hipótesis actuales implican claramente que la señalización defectuosa de la insulina en el cerebro contribuye a la disfunción sináptica y los déficits cognitivos en la EA, la toma de antidiabéticos podría actuar como protector en la EA.

VI. Variables más relevantes en los mejores modelos

Para concluir con los resultados se puede resumir la información de los diferentes modelos de la siguiente manera: La variable ictus es considerada como la más relevante, apareciendo en todos los clasificadores y prediciendo como única variable en todos los clasificadores un 74.87%. La variable hipertensión arterial como se ha visto anteriormente también constituye una variable importante en el clasificador SVM, apareciendo en casi todos sus modelos. En cuanto a la toma de antiarrítmicos, se considera en todos los clasificadores como un factor protector, una afirmación considerada y avalada por la literatura científica que prueba la eficacia de los medicamentos antiarrítmicos para la mejora de patologías cardíacas. Por último, la variable fumador genera controversia en los distintos modelos, ya que en unos clasifica como factor protector y en otros como factor de riesgo de la EA. Resultados que concuerdan también con la literatura, donde en algunos estudios se asocia la nicotina como

factor protector contra la EA (538) y en otros estudios se considera ser fumador como factor de riesgo de la EA (486,490).

CONCLUSIONS SECTION 2

"Miradas perdidas, sueños robados, mentes que olvidan, sentimientos encontrados.".

(Diego Pérez)

CONCLUSIONS SECTION 2

AD is a devastating syndrome that affects an increasing number of people due to the aging worldwide population. According to Alzheimer's Disease International (ADI), 24.3 million people were living with dementia in 14 World Health Organization (WHO) regions in 2001, and this will reach 81.1 million by 2040, with numbers doubling every 20 years (88).

The diagnosis of AD during a patient's lifetime has always been achieved on the basis of clinical criteria and associated diagnostic algorithms, such as those presented by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984). These criteria had a high measure of sensitivity, but because they did not reach 100%, the diagnosis was always defined as "probable" or "possible" AD.

The first chapter explains the methodology for developing a system to generate models from medical diagnoses established in a database, considering that these models must be simple and that few variables have been selected from among a big data base. These variables should be really relevant. The tool developed in this first chapter is a variable selection method for diagnostic problems that is combined with different types of classifiers. In our case, we consider linear classifiers, since they are more easily interpretable, specifically Linear Discriminant Analysis (LDA), Logistic Regression (LR), and Support Vector Machine (SVM).

Through the application of different computational tests, the best performance of the generated tool is demonstrated compared to other variable selection methods existing in the literature. The aim of this chapter is to search more efficient and accurate models that establish the diagnosis of AD.

The second chapter describes the approach to a research problem aimed at applying the algorithm described in the previous chapter to detect the probable appearance of AD in its first phase, using autonomous learning or Machine Learning techniques. A database of two groups (subjects diagnosed with AD and healthy subjects) was considered and classified between these two groups. After group separation, a Machine Learning algorithm was implemented for classification that determined different results.

The stroke variable was the most relevant variable. In this case, stroke predict at 74.87% in all classifiers and it is the only variable with these results. Arterial hypertension also constituted an important variable in the SVM classifier, appearing in almost all the models. Antiarrhythmic drugs were considered a protective factor in all classifiers, a statement considered and supported by the scientific literature. Along the same lines as the previous variable, the use of beta-blocking drugs also decreased the probability of suffering from AD, and this is shown in the results presented, where this variable increased the hit ratio in all the classifiers presented. Finally, the smoking variable generates controversy in the different models, since in some it is classified as a protective factor and in others as a risk factor for AD. The results on the relationship between AD and these drugs (antiarrhythmics and beta-blockers) are also consistent with the literature.

Among the contributions of this section, this is the first time that ADL, RL, and SVM models are jointly applied to predict the clinical diagnosis of AD using clinical information (lifestyle, diagnosed pathologies, medication intake, and filial data). The encouraging results of this study suggest the feasibility of a more comprehensive and extensive approach to predicting and assisting clinical diagnosis by Machine Learning methods. Medicine is always advancing and is always trying to optimize processes in the prevention, diagnosis, treatment, and care of diseases of all kinds and, in this case, the project contributes directly to the field of neurology. Thanks to the results of this study, it is possible not only to prevent, but also to

treat, diagnose, and cope with AD even before its onset. Another point to highlight is that the technological field, and specifically Machine Learning enriched this study providing solutions to problems of all kinds, in this case a problem of medical diagnosis, which can be handled through predictive models of Machine Learning, leaving the door open to endless technological possibilities directly in this field and derivatives thereof. Another important contribution is that the algorithm for the early detection of AD is non-invasive – it does not require any examination of or procedure on the patient; it is based exclusively on the patient's medical history. Therefore, it is quite easy to use and implement.

In terms of limitations, it would be advisable to carry out the study with a larger number of cases incorporated in the database, which would allow for the inclusion of cross-validation, with which more generalizable conclusions would be obtained. In this sense, if an investigation were carried out with a larger sample of cases, it is very likely that this new database would make it possible to generate more stable and more generalizable results.

FUTURE LINES

Early diagnosis of AD is very important nowadays. In addition, noninvasive diagnostic methods based mainly on patient history, clinical observation, and cognitive assessment could help to control the development of AD. In this regard, different diagnostic methods have been used where the accuracy of the performance of each classifier in the method is successful. This novel method, at best, has a classification accuracy of approximately 82.36% in a model with 5 variables. Other models need a larger number of variables to achieve improved prediction by a further 2%.

Prevention of AD remains an important goal due to its high prevalence in society. These results suggest the critical importance of interventions targeting modifiable risk factors to improve AD prevention and the complex relationships between different risk factors and AD, as previously shown by another research. Cognitive engagement, diet/nutritional

supplement intake, level of physical activity, type 2 diabetes, level of alcohol consumption, mood disorders, hypertension, hypercholesterolemia, and smoking have been proposed as modifiable risk factors for AD. Further studies with longitudinal assessment and a broader set of variables are currently needed to be able to determine more conclusive results.

Future lines of research are established, such as studying the results of the relationship between AD and smoking. Most studies in the literature show that smoking may not be related to the onset of AD or increase the risk of developing AD, but do not specifically address the possible long-term effects that could be obtained from nicotinic receptor modulation in AD. Cigarette smoke is known to contain many chemicals and substances, making it impossible to assess how nicotinic modulation alone could alter AD risk. In addition, it is proposed to continue with the study of cardiovascular risk factors. In this chapter, risk factors have become particularly relevant in the relationship with AD.

FINAL CONCLUSIONS

CONCLUSIONS

"Yo te quitaré tus ojos y los pondré en lugar de los míos, tú me quitarás mis ojos y los pondrás en lugar de los tuyos, así yo podré verte con tus propios ojos y tú me verás a mí con los míos.".

(Jesús de la Gándara)

FINAL CONCLUSIONS

In recent years, there have been important advances in scientific research on AD. With the realization that this disease causes brain damage even up to 15 to 20 years after the onset of the first symptoms, research has focused on the prevention of its development. National experts Bermejo-Pareja et al. (336), and international (539) recommend primary and secondary prevention studies aimed at healthy people or those with very mild symptomatology. It is considered essential to intervene before significant neuronal loss occurs which leads to the onset of AD. In the UK, only 5% of research funding between 1990 and 2012 was invested in risk factors and preventive strategies, 11% in dementia diagnosis, 20% in care and support, while nearly 65% was invested in etiology, cure, and treatment development (540). However, this trend is changing in recent years, and resources are being redirected to research on preventive strategies (541).

Disappointing results of drugs tested to-date in clinical trials to modify the course of mild/moderate AD, combined with clear epidemiological evidence of its risk factors, are contributing to the development of primary prevention initiatives (542). As a consequence, many intervention studies are currently focusing on cognitively healthy individuals as the best strategy to reduce the incidence and prevalence of AD. On the other hand, the characterization of the long asymptomatic stage of AD is enabling the development of intervention studies and secondary prevention programs in asymptomatic at-risk individuals, before substantial irreversible neuronal dysfunction and loss occurs, an approach that emerges as highly relevant (542). In this sense, this thesis addresses both primary and secondary prevention of AD.

In the first section, specific estimates of the effect sizes of the association between different modifiable risk factors and AD are provided using meta-analytic techniques that are the basis for the establishment of primary prevention programs, as well as for the review of

current strategies at this level. Using this focus on risk factors, Norton et al. (466) concluded that about one third of new cases of AD worldwide could be attributable to these factors and, consequently, could be prevented. These researchers estimated that decreasing the prevalence of seven risk factors (diabetes mellitus, hypertension and obesity in middle age, physical inactivity, depression, smoking, and low education) by 10% to 20% per decade could reduce the prevalence of AD in 2050 by 8% to 15%, or between 8.8 million and 16.2 million cases. Therefore, the incidence of AD could be reduced with the use of effective measures aimed at reducing the prevalence of some of the cardiovascular risk factors examined in this thesis, such as stroke, hypertension, cholesterol, and depression (528). Observational evidence provides a solid basis for identifying vascular and lifestyle-related risk factors that increase the risk of developing AD. We conclude that even modest reductions in these factors can significantly mitigate the overall risk and delay the age of onset of AD (539).

The use of "health promotion and prevention" techniques to promote a healthy lifestyle with the aim of avoiding the development of risk factors can be particularly effective in terms of reducing the risk of contracting AD. This lifestyle refers to a series of daily attitudes and behaviors that people perform to stay healthy, such as regular physical activity, weight control, avoiding or reducing the consumption of alcohol or other drugs, eating a balanced diet, promoting regular and quality sleep, stimulating the mind, maintaining an active social life, and taking care of mental health. Interventions aimed at promoting these habits to reduce the predisposition to develop modifiable risk factors (such as cardiovascular disease or depression) can play a key role in preventing and delaying functional decline, ultimately reducing the incidence of AD.

In two longitudinal studies (543) with 5.8- and 6-year follow-ups, the hazard ratio for AD in 2 cohorts was 0.73 (95 % CI 0.66-0.80) for each additional healthy lifestyle factor (no

smoking, mild to moderate alcohol consumption, ≥150 min/week of moderate/vigorous intensity physical activity, a high-quality Mediterranean diet, and participation in cognitive activities in old age). In the first group, participants with 0 to 1 healthy lifestyle factor, the risk of AD was 37 % lower (combined HR 0.63, 95 % CI 0.47-0.84), than in the group with 2 to 3 healthy lifestyle factors. In the group with 4 to 5 healthy lifestyle factors, it was 60 % lower (pooled HR 0.40, 95 % CI 0.28-0.56). Likewise, large epidemiological cohort studies suggest that the incidence of age-specific dementia is decreasing in high-income countries, probably due to better control of cardiovascular risk factors (541,544,545). It is concluded that promoting a healthy lifestyle is associated with a substantially lower risk of Alzheimer's dementia.

In summary, the results of Section 1 contribute to design guidelines for public health policy since the estimates found in the different studies could support decisions on health education and community planning. Promotion and prevention agendas linking AD with other noncommunicable diseases should be developed to help optimize preventive strategies. It is emphasized that an effective strategy for the primary prevention of AD aimed at the general population should establish, on the one hand, risk factor surveillance programs in different age groups and, on the other hand, focus on how to manage lifestyle and cardiovascular risk factors. Along these lines, if an adequate epidemiological surveillance system is established, it would be useful to cover all the risk factors associated with AD to increase the possibility of preventing AD. In this sense, epidemiological surveillance is understood as the systematic and continuous collection of information to design, monitor, and evaluate different public health interventions (546). Furthermore, with AD being a multifactorial disorder, interventions that promote healthy lifestyles should simultaneously target multiple risk factors. Reliable estimates of the distribution of risk factors by world region and their long-term trends are crucial to better understand the impact of these factors on the health outcomes of future generations of older adults (547).

Section 2 deals with secondary prevention aimed at the early diagnosis of AD. With this objective, first, a specific methodology is described to develop a model generator system from medical diagnoses established in a database. The tool developed is a variable selection method for diagnosis problems that is combined with different types of classifiers. In this case, linear classifiers were considered: Discriminant Analysis (DLA), Logistic Regression (LR), and Support Vector Machine (SVM). In the chapter 7, the algorithm described in the chapter 6 was applied, with results that made it possible to detect the probable occurrence of AD using autonomous learning or Machine Learning techniques. Thus, different variables have been established (stroke, arterial hypertension, and cholesterol as risk factors and antiarrhythmic and beta-blocker drugs for the improvement of different cardiac pathologies as protective factors) that predict a high probability of developing AD and that can lay the foundations for defining a scientific methodology that allows its early diagnosis. In short, once the presence of a series of combined risk and protective factors has been diagnosed, it is possible to intervene early to reduce the risk of developing AD in the future. The preclinical stage may offer the optimal window for therapeutic success and the opportunity to intervene earlier in the continuum, halting or delaying the onset of cognitive decline and, ultimately, AD dementia (542).

As noted, there is increasing evidence that the molecular mechanisms of AD are activated several years before neurons begin to die and cognitive deficits become apparent. Thus, one of the most important challenges today is the need for such early and accurate diagnostics of AD (548). Several reasons reinforce this line of intervention. On the one hand, the diagnosis of AD consists of the evaluation of clinical symptoms; and on the other hand, the diagnosis of AD is based on the evaluation of clinical symptoms (549), so the person is usually diagnosed when dementia is ongoing (550). This is the case for standardized clinical criteria, such as the Diagnostic and Statistical Manual of Mental Disorders and the National Institute of Neurological, Communicative Disorders, and Stroke-AD and Related Disorders

Association (NINCDS-ADRDA) definitions. In addition, neuropsychological tests, such as the cognitive subscale of the AD Assessment Scale (ADAS Cog), are used to monitor the progression of AD symptoms. Although it is unquestionable that these tests reflect an important aspect in the diagnosis and progression of the disease, the ceiling effects in 8 of the 11 items and their low test-retest reliability in some of the items (intraclass correlation coefficients between 0.5 and 0.8) in patients with mild AD make it necessary that other diagnostic options be investigated (551). On the other hand, the use of biomarkers, neuroimaging, and DNA testing (552) to generate an accurate preclinical diagnosis would be too expensive to apply to the entire population of elderly people at risk of dementia. Hence the importance of developing a high accuracy tool that can detect AD before the onset of the first symptoms. In response to the need for early AD diagnosis, this thesis has created an easy-to-use and inexpensive tool by combining different variables to accurately determine the likelihood of developing AD.

Currently, some pharmacological treatments used in AD can only treat the symptoms, but not change its course. Despite advances in the pathophysiology of AD, such as the functioning of amyloid and tau, or the understanding of the causal mechanisms of AD pathology, effective treatment remains elusive (550). Therefore, since there are no effective treatment options for many patients, early diagnosis would help to detect AD early and, in this way, propose a treatment that can delay its progression. Currently, early intervention is the most optimal strategy because the patient's level of function is preserved for a longer period of time (542). In this regard, the efforts of a multitude of researchers to develop effective diagnostic tools and modifying therapies for AD have shown that it is a pathology frequently associated with other variables. Defining the relationships between various co-pathologies and their interdependence remains an active area of research (553).

There is previous experience studying the efficacy of long-term multidomain interventions in individuals identified to be at increased risk of developing AD (e.g., individuals diagnosed with several of the risk factors associated with AD). FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) is a 2-year multicenter randomized controlled trial conducted in Europe that examined the efficacy of 2-year multidomain lifestyle intervention (dietary counseling, vascular risk monitoring, exercise, and cognitive training) in 1260 participants aged 60 to 77 years at increased risk of dementia. Participation in the intervention was associated with neuropsychological improvements and in all cognitive subdomains. Lifestyle improvement was associated with overall neuropsychological improvement and in executive function, but not in other cognitive domains. According to this study, it is important to provide sufficiently intensive lifestyle interventions and to emphasize measures that support healthy lifestyle adherence to promote good cognitive functioning (545). In the ACTIVE (Advanced Cognitive Training for Independent and Vital Elderly) study realized in EE.UU (554) with people over 65 at risk of functional decline, but who had not yet experienced functional decline (at trial entry had no significant cognitive, physical, or functional impairment), showed that, after 10 years of follow-up, rates of dementia in those who received some cognitive intervention (specific training in memory, reasoning, or processing speed) were significantly lower for participants in the processing speed intervention group (555). However, all trials have not shown positive results. The MAPT (Multidomain Alzheimer Preventive Trial) is a three-year randomized controlled trial conducted in France that combines a multidomain lifestyle-based intervention (nutrition counseling, physical activity, and cognitive training) with a nutraceutical compound (omega-3 fatty acid supplements) (7) targeting 1680 people aged 70 years or older who had subjective complaints of memory, limitation in an instrumental activity of daily living, or slow walking speed. The trial was not effective in mitigating cognitive decline (556). PreDIVA (Prevention of Dementia by Intensive Vascular care),

conducted in the Netherlands, is a six-year study of 3526 older adults aged 70 to 78 years who received a nurse-led multidomain intervention consisting of healthy lifestyle and intensive vascular care advice and risk factor management, including initiation or optimization of antithrombotic and pharmacological treatments for hypertension, dyslipidemia, or diabetes, when necessary (8). The main results of the trial showed no difference in the incidence of dementia between the intervention and control groups (557,558).

Having a method that can make an early diagnosis of AD can translate into an improvement for the individual, the caregiver, and society, as well as a reduction in the risk of developing the disease or delaying its progression. In addition, early diagnosis of AD is important to give the individual and their caregivers time to make decisions and plan, and to provide access to treatments that can help control symptoms. In Spain, work is being done on how to diagnose AD earlier, so there is now more diversified research on Alzheimer's that could open the door to a solution to this disease (559). For example, PREDIMED (Prevention with Mediterranean Diet) is a parallel group randomized clinical trial of 447 cognitively healthy volunteers from Barcelona (233 women [52.1 %]; mean age, 66.9 years) at high cardiovascular risk randomized to a nutritional intervention (Mediterranean diet supplemented with extra virgin olive oil, Mediterranean diet supplemented with mixed nuts, or control diet based on advice to reduce dietary fat). The benefit of the Mediterranean diet was independent of sex, age, energy intake, and variables related to cognition, including educational level, APOE ε4 genotype, and vascular risk factors (560).

In summary, Section 2 provided empirical evidence to support a series of recommendations aimed at developing strategies that promote early diagnosis and earlier interventions both to save health care costs and to improve quality of life. On the one hand, epidemiological surveillance focused on the combined risk factors that increase the probability of developing

AD, such as stroke, arterial hypertension, and cholesterol. The surveillance system should allow information to be collected systematically, uniformly, of sufficient quality, and permanently (or with determined periodicities) (561). On the other hand, interventions aimed at improving the cardiovascular risk profile with both pharmacological (e.g., antiarrhythmic drugs or beta-blockers) and non-pharmacological (healthy lifestyle recommendations and information on adherence to lifestyle changes) treatments are required to prevent the development of AD in people at risk of cognitive impairment.

In this thesis, several risk factors have been postulated as determinants for predicting the development of AD. Some of these factors are associated with people's lifestyles. From this perspective, we wanted to highlight occupation as a protective factor that could contribute to new ideas focused on the prevention of these risk factors to avoid or delay the onset of AD. Occupational therapy can play a fundamental role in the promotion of occupations and healthy lifestyles that improve an individual's aging process. Occupational therapy would allow maintaining functionality, improving the quality of life of the person and his or her environment, and slowing the progression of the disease (562). Occupational therapy can represent an important part of the treatment as it increases the autonomy of people, allowing for the development of activities of daily living through cognitive and behavioral exercises (70). The lifestyle habits and occupations that people engage in can reduce or increase the risk of factors that progress to the development of AD. This is why occupational therapy can contribute to the primary and secondary prevention approach to AD (74). Specifically, in the case of secondary prevention, the results of this thesis suggest that, together with encouraging adherence to a healthy lifestyle, people diagnosed with any of the risk factors should follow pharmacological treatment to reduce the probability of developing AS, such as antiarrhythmic drugs to prevent arrhythmias derived from different cardiovascular diseases (such as heart problems or high blood pressure, and even high cholesterol levels).

To conclude, this thesis applies diverse methodologies with different samples to demonstrate the predictive robustness of risk factors associated with the development of AD with the aim of contributing to its prevention. It is hoped that primary and secondary prevention will reduce the number of people suffering from this disease, alleviating an enormous burden on the public health of countries around the world. The costs of neurodegenerative diseases such as AD are high, and it seems likely that these resources and techniques can be used to reduce the incidence and prevalence of AD. Thus, epidemiological evidence of AD risk factors contributes to and encourages the development of prevention initiatives. From this perspective, the results derived from current trials and strategies are needed to improve future designs by performing a post-hoc analysis of the potential benefits of risk factor reduction on disease incidence (542).

REFERENCIAS BIBLIOGRÁFICAS

REFERENCIAS BIBLIOGRÁFICAS

1. Bravo MJR, Fernández RO. Estimulación cognitiva en la enfermedad de Alzheimer: ejercicios prácticos. Formacion Alcala S.L; 2010.

2. Maurer K, Maurer U. Alzheimer. La vida de un médico y la historia de una enfermedad. Ediciones Díaz de Santos; 2006.

3. Martin P, Anders W, Maëlenn G. World Alzheimer report 2015: the global impact of dementia. Alzheimer's Dis Int ADI Lond. 2015.

2. Leyhe T, Reynolds CF III, Melcher T, Linnemann C, Klöppel S, Blennow K, et al. A common challenge in older adults: Classification, overlap, and therapy of depression and dementia. Alzheimers Dement [Internet]. 2017;13(1):59–71. Disponible en: http://dx.doi.org/10.1016/j.jalz.2016.08.007

3. Donoso A. La enfermedad de Alzheimer. Rev Chil Neuro-Psiquiatr. 2003; 41:13-22. Disponible en: https://doi.org/10.4067/S0717-92272003041200003

4. Rodrigues CYDS, Figueiredo PAC. Estado conductual y psiquiátrico en el adulto mayor con trastorno neurocognitivo leve de enfermedad de alzheimer posible. Enseñ E Investig En Psicol. 2017;22(3):373-379. Disponible en: https://www.redalyc.org/articulo.oa?id=29255775011

5. INE. Defunciones según la causa de muerte. Notas de prensa. [Internet]. 2016. Disponible en: www.ine.es/prensa/prensa.htm

6. Liu Y, Zhong X, Shen J, Jiao L, Tong J, Zhao W, et al. Elevated serum TC and LDL-C levels in Alzheimer's disease and mild cognitive impairment: A meta-analysis study. Brain Res. 15 de enero de 2020; 1727:146554. Disponible en: https://doi.org/10.1016/j.brainres.2019.146554

7. Santabarbara J, Sevil-Perez A, Olaya B, Gracia-Garcia P, Lopez-Anton R. Depresión tardía clínicamente relevante y riesgo de demencia: revisión sistemática y metaanálisis de

estudios prospectivos de cohortes. Rev Neurol [Internet]. 2019;68(12):493–502. Disponible en: http://dx.doi.org/10.33588/rn.6812.2018398

8. Ford E, Greenslade N, Paudyal P, Bremner S, Smith HE, Banerjee S, et al. Predicting dementia from primary care records: A systematic review and meta-analysis. PLoS ONE [Internet]. 29 de marzo de 2018 [citado 9 de febrero de 2020];13(3). Disponible en: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5875793/ https://doi.org/10.1371/journal.pone.0194735

9. Kuring JK, Mathias JL, Ward L. Prevalence of depression, anxiety and PTSD in people with dementia: A systematic review and meta-analysis. Neuropsychol Rev [Internet]. 2018;28(4):393–416. Disponible en: http://dx.doi.org/10.1007/s11065-018-9396-2

10.Cherbuin N, Kim S, Anstey KJ. Dementia risk estimates associated with measures of depression: a systematic review and meta-analysis. BMJ Open [Internet]. 2015 [citado el 8 de marzo de 2023];5(12): e008853. Disponible en: https://bmjopen.bmj.com/content/5/12/e008853.short

11.Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF 3rd. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry [Internet]. 2013;202(5):329–35. Disponible en: http://dx.doi.org/10.1192/bjp.bp.112.118307

12.Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies: Diabetes and cognitive function. Intern Med J [Internet]. 2012;42(5):484–91. Disponible en: http://dx.doi.org/10.1111/j.1445-5994.2012.02758.x

13.Guan JW, Huang CQ, Li YH, Wan CM, You C, Wang ZR, et al. No Association Between Hypertension and Risk for Alzheimer's Disease: A Meta-Analysis of Longitudinal Studies. J Alzheimers Dis. 1 de enero de 2011;27(4):799-807. Disponible en: https://doi.org/10.3233/JAD-2011-111160

14.Béjot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. Presse Med [Internet]. 2016;45(12 Pt 2): e391–8. Disponible en: https://www.sciencedirect.com/science/article/pii/S0755498216303098

15.Béjot Y, Daubail B, Giroud M. Epidemiology of stroke and transient ischemic attacks: Current knowledge and perspectives. Rev Neurol (Paris) [Internet]. 2016;172(1):59–68. Disponible en: https://www.sciencedirect.com/science/article/pii/S0035378715009248

16.Kuźma E, Lourida I, Moore SF, Levine DA, Ukoumunne OC, Llewellyn DJ. Stroke and dementia risk: a systematic review and meta-analysis. Alzheimers Dement. 2018;14(11):1416-26. Disponible en: https://doi.org/10.1016/j.jalz.2018.06.3061

17.Thiel A, Cechetto DF, Heiss WD, Hachinski V, Whitehead SN. Amyloid burden, neuroinflammation, and links to cognitive decline after ischemic stroke. Stroke. 2014;45(9):2825-9. Disponible en: https://doi.org/10.1161/STROKEAHA.114.004285

18.Cechetto DF, Hachinski V, Whitehead SN. Vascular risk factors and Alzheimer's disease. Expert Rev Neurother. 1 de mayo de 2008;8(5):743-50. Disponible en: https://doi.org/10.1586/14737175.8.5.743

19.Meilán JJG, Gutiérrez JMC. Enfermedad de Alzheimer y otras demencias neurodegenerativas: Aspectos psicosociales. Elsevier España; 2017.

20.Abizanda P, Jordán J. Conocer para aceptar. Enfermedad de Alzheimer. Cuenca: Ediciones de la Universidad de Castilla-La Mancha; 2011.

21.INE. Proyecciones de población. Notas de prensa. [Internet]. 2018. Disponible en: https://www.ine.es/dyngs/Prensa/notasPrensa.htm

22.INE. Proyecciones de población. Notas de prensa. [Internet]. 2022. Disponible en: https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736176953&menu=ultiDatos&idp=1254735572981

23.Nolasc Acarín AM. Alzheimer: envejecimiento y demencia. 1a edición. Barcelona: RBA; 2017.

24.Fuentes P. Enfermedad de Alzheimer: una nota histórica. Rev Chil Neuro-Psiquiatr. 2003; 41:9-12. Disponible en: https://doi.org/10.4067/S0717-92272003041200002

25.Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Med. 21 de julio de 2009;6(7): e1000097. Disponible en: https://doi.org/10.1371/journal.pmed.1000097

26.Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 15 de febrero de 2007;7(1):10. Disponible en: https://doi.org/10.1186/1471-2288-7-10

27.Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol. 1 de octubre de 2009;62(10):1013-20. Disponible en: https://doi.org/10.1016/j.jclinepi.2008.10.009

28.Zhou J, Yu JT, Wang HF, Meng XF, Tan CC, Wang J, et al. Association between stroke and Alzheimer's disease: systematic review and meta-analysis. J Alzheimers Dis. 2015;43(2):479-89. Disponible en: https://doi.org/10.3233/JAD-140666

29.Zhou Z, Liang Y, Zhang X, Xu J, Lin J, Zhang R, et al. Low-density lipoprotein cholesterol and Alzheimer's disease: a systematic review and meta-analysis. Front Aging Neurosci. 2020; 12:5. Disponible en: https://doi.org/10.3389/fnagi.2020.00005

30.Wu Y, Wang Z, Jia X, Zhang H, Zhang H, Li J, et al. Prediction of Alzheimer's disease with serum lipid levels in Asian individuals: a meta-analysis. Biomarkers. 19 de mayo de 2019; 24(4):341-51. Disponible en: https://doi.org/10.1080/1354750X.2019.1571633

31.Santabarbara J, Pérez AS, Olaya B, Gracia-García P, Antón RL. Depresión tardía clínicamente relevante y riesgo de demencia: revisión sistemática y metaanálisis de estudios prospectivos de cohortes. Rev Neurol. 2019;68(12):493-502. Disponible en: https://doi.org/10.33588/rn.6812.2018398

32.Kuring JK, Mathias JL, Ward L. Risk of Dementia in persons who have previously experienced clinically-significant Depression, Anxiety, or PTSD: A Systematic Review and Meta-Analysis. J Affect Disord. 1 de septiembre de 2020; 274:247-61. Disponible en: https://doi.org/10.1016/j.jad.2020.05.020

33.Cherbuin N, Kim S, Anstey KJ. Dementia risk estimates associated with measures of depression: a systematic review and meta-analysis. BMJ Open. 2015;5(12). Disponible en: https://doi.org/10.1136/bmjopen-2015-008853

34.Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry. mayo de 2013;202(5):329-35. Disponible en: https://doi.org/10.1192/bjp.bp.112.118307

35.Gao Y, Huang C, Zhao K, Ma L, Qiu X, Zhang L, et al. Retracted: Depression as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Int J Geriatr Psychiatry. 2013;28(5):441-9. Disponible en: https://doi.org/10.1002/gps.3845

36.Profenno LA, Porsteinsson AP, Faraone SV. Meta-Analysis of Alzheimer's Disease Risk with Obesity, Diabetes, and Related Disorders. Biol Psychiatry. 15 de marzo de 2010;67(6):505-12. Disponible en: https://doi.org/10.1016/j.biopsych.2009.02.013

37.Cheng J, Liu HP, Lee CC, Chen MY, Lin WY, Tsai FJ. Matrix metalloproteinase 14 modulates diabetes and Alzheimer's disease cross-talk: a meta-analysis. Neurol Sci. 1 de febrero de 2018;39(2):267-74. Disponible en: https://doi.org/10.1007/s10072-017-3166-4

38.Vagelatos NT, Eslick GD. Type 2 Diabetes as a Risk Factor for Alzheimer's Disease: The Confounders, Interactions, and Neuropathology Associated With This Relationship. Epidemiol Rev. 1 de enero de 2013;35(1):152-60. Disponible en: https://doi.org/10.1093/epirev/mxs012

39. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. J Diabetes Investig. 2013;4(6):640-50. Disponible en: https://doi.org/10.1111/jdi.12087

40.Meng XF, Yu JT, Wang HF, Tan MS, Wang C, Tan CC, et al. Midlife Vascular Risk Factors and the Risk of Alzheimer's Disease: A Systematic Review and Meta-Analysis. J Alzheimers Dis. 1 de enero de 2014;42(4):1295-310. Disponible en: https://doi.org/10.3233/JAD-140954

41.Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2015;86(12):1299-306. Disponible en: https://doi.org/10.1136/jnnp-2015-310548

42.Zhang J, Chen C, Hua S, Liao H, Wang M, Xiong Y, et al. An updated meta-analysis of cohort studies: Diabetes and risk of Alzheimer's disease. Diabetes Res Clin Pract. 1 de febrero de 2017; 124:41-7. Disponible en: https://doi.org/10.1016/j.diabres.2016.10.024

43.Kivimäki M, Singh-Manoux A, Pentti J, Sabia S, Nyberg ST, Alfredsson L, et al. Physical inactivity, cardiometabolic disease, and risk of dementia: an individual-participant meta-analysis. BMJ [Internet]. 2019 [citado el 8 de marzo de 2023];365: l1495. Disponible en: https://www.bmj.com/content/365/bmj.l1495.short

44.Wang ZT, Xu W, Wang HF, Tan L, Tan CC, Li JQ, et al. Blood pressure and the risk of dementia: a dose-response meta-analysis of prospective studies. Curr Neurovasc Res. 2018;15(4):345-58. Disponible en: https://doi.org/10.2174/1567202616666181128114523

45.Beydoun MA, Beydoun HA, Gamaldo AA, Teel A, Zonderman AB, Wang Y. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. BMC Public Health. 2014;14(1):1-33. Disponible en: https://doi.org/10.1186/1471-2458-14-643

46.Zhong G, Wang Y, Zhang Y, Guo JJ, Zhao Y. Smoking is associated with an increased risk of dementia: a meta-analysis of prospective cohort studies with investigation of potential

effect modifiers. Laws K, editor. PLOS ONE. 12 de marzo de 2015;10(3): e0118333. Disponible en: https://doi.org/10.1371/journal.pone.0118333

47.Peters R, Poulter R, Warner J, Beckett N, Burch L, Bulpitt C. Smoking, dementia and cognitive decline in the elderly, a systematic review. BMC Geriatr. 2008;8(1):1-7. Disponible en: https://doi.org/10.1186/1471-2318-8-36

48.Fontelles MJ, Carvalho RM de, D'Oliveira MS. Alcoholism and smoking as a risk factor for late-onset Alzheimer's disease: a meta-analysis study. Rev Para Med. 2007;7-13. Disponible en: https://doi.org/10.5123/S0101-59072007000100002

49.Chen H, Xue W, Li J, Fu K, Shi H, Zhang B, et al. 25-Hydroxyvitamin D levels and the risk of dementia and Alzheimer's Disease: a dose-response meta-analysis. Front Aging Neurosci. 2018; 10:368. Disponible en: https://doi.org/10.3389/fnagi.2018.00368

50.Chai B, Gao F, Wu R, Dong T, Gu C, Lin Q, et al. Vitamin D deficiency as a risk factor for dementia and Alzheimer's disease: an updated meta-analysis. BMC Neurol. 2019;19(1):1-11. Disponible en: https://doi.org/10.1186/s12883-019-1500-6

51.Yang K, Chen J, Li X, Zhou Y. Vitamin D concentration and risk of Alzheimer disease: A meta-analysis of prospective cohort studies. Medicine (Baltimore). 2019;98(35). Disponible en: https://doi.org/10.1097/MD.0000000000016804

52.Jayedi A, Rashidy-Pour A, Shab-Bidar S. Vitamin D status and risk of dementia and Alzheimer's disease: a meta-analysis of dose-response. Nutr Neurosci. 2019;22(11):750-9. Disponible en: https://doi.org/10.1080/1028415X.2018.1436639

53.Wang W, Li J, Zhang H, Wang X, Zhang X. Effects of vitamin E supplementation on the risk and progression of AD: a systematic review and meta-analysis. Nutr Neurosci. 2019;1-10. Disponible en: https://doi.org/10.1080/1028415X.2019.1585506

54. Doets EL, van Wijngaarden JP, Szczeciñska A, Dullemeijer C, Souverein O, Dhonukshe-Rutten RA, et al. Vitamin B12 intake and status and cognitive function in elderly people: a

systematic review with meta-analyses. Approaches Setting Micronutr Recomm. 2011;109. Disponible en: https://doi.org/10.1093/epirev/mxs003

55.Wang HL, Wang YY, Liu XG, Kuo SH, Liu N, Song QY, et al. Cholesterol, 24-Hydroxycholesterol, and 27-Hydroxycholesterol as surrogate biomarkers in cerebrospinal fluid in mild cognitive impairment and Alzheimer's Disease: A meta-analysis. J Alzheimers Dis. 1 de enero de 2016;51(1):45-55. Disponible en: https://doi.org/10.3233/JAD-150734

56.Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Intern Med J. 2012;42(5):484-91. Disponible en: https://doi.org/10.1111/j.1445-5994.2012.02758.x

57.Anstey K, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obes Rev. 2011;12(5): e426-37. Disponible en: https://doi.org/10.1111/j.1467-789X.2010.00825.x

58.Lennon MJ, Makkar SR, Crawford JD, Sachdev PS. Midlife Hypertension and Alzheimer's Disease: a systematic review and meta-analysis. J Alzheimers Dis. 1 de enero de 2019;71(1):307-16. Disponible en: https://doi.org/10.3233/JAD-190474

59.Wolters FJ, Segufa RA, Darweesh SKL, Bos D, Ikram MA, Sabayan B, et al. Coronary heart disease, heart failure, and the risk of dementia: A systematic review and meta-analysis. Alzheimers Dement. 1 de noviembre de 2018;14(11):1493-504. Disponible en: https://doi.org/10.1016/j.jalz.2018.01.007

60.Launer L, White L, Petrovitch H, Ross G, Curb J. Cholesterol and neuropathologic markers of AD: a population-based autopsy study. Neurology. 2001;57(8):1447-52. Disponible en: https://doi.org/10.1212/WNL.57.8.1447

61.Tan ZS, Seshadri S, Beiser A, Wilson PW, Kiel DP, Tocco M, et al. Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham Study. Arch Intern Med. 2003;163(9):1053-7. Disponible en: https://doi.org/10.1001/archinte.163.9.1053

62. Green RC, Cupples LA, Kurz A, Auerbach S, Go R, Sadovnick D, et al. Depression as a Risk Factor for Alzheimer Disease: The MIRAGE Study. Arch Neurol. 1 de mayo de 2003;60(5):753-9. Disponible en: https://doi.org/10.1001/archneur.60.5.753

63.Kessing LV, Søndergård L, Forman JL, Andersen PK. Antidepressants and dementia. J Affect Disord. 1 de septiembre de 2009;117(1):24-9. Disponible en: https://doi.org/10.1016/j.jad.2008.11.020

64.Richardson K, Fox C, Maidment I, Steel N, Loke YK, Arthur A, et al. Anticholinergic drugs and risk of dementia: case-control study. BMJ [Internet]. 25 de abril de 2018 [citado 1 de diciembre de 2020];361. Disponible en: https://doi.org/10.1136/bmj.k1315

65.Wang C, Gao S, Hendrie HC, Kesterson J, Campbell NL, Shekhar A, et al. Antidepressant use in the elderly is associated with an increased risk of dementia. Alzheimer Dis Assoc Disord. 2016;30(2):99-104. Disponible en: https://doi.org/10.1097/WAD.0000000000000103

66.Pedditizi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. Age Ageing [Internet]. 2016 [citado el 8 de marzo de 2023];45(1):14–21. Disponible en: https://academic.oup.com/ageing/article/45/1/14/2195252?login=false

67.Aranceta J, Pérez Rodrigo C, Majem LS, Barba LR, Izquierdo JQ, Vioque J, et al. Prevalencia de la obesidad en España: resultados del estudio SEEDO 2000. Med Clin (Barc) [Internet]. 2003;120(16):608–12. Disponible en: https://www.sciencedirect.com/science/article/pii/S0025775303737877

68.Matilla-Mora R, Martínez-Piédrola RM, Fernández Huete J. Eficacia de la terapia ocupacional y otras terapias no farmacológicas en el deterioro cognitivo y la enfermedad de Alzheimer. Rev Esp Geriatría Gerontol. 1 de noviembre de 2016;51(6):349-56. Disponible en: https://doi.org/10.1016/j.regg.2015.10.006

69.García BM. Terapias no farmacológicas para los síntomas psicológicos y conductuales de la enfermedad de Alzheimer. Rev Astur Ter Ocupacional. 2018;(13):1-12. Disponible en: https://dialnet.unirioja.es/servlet/articulo?codigo=6562812

70.Bermejo-Pareja F, Llamas-Velasco S, Villarejo-Galende A. Prevención de la enfermedad de Alzheimer: un camino a seguir. Rev Clínica Esp. 1 de diciembre de 2016;216(9):495-503. Disponible en: https://doi.org/10.1016/j.rce.2016.05.010

71.Peyronnet M. Prevenir el alzheimer. Editorial HISPANO EUROPEA; 2011.

72.Castro JMA. La ocupación como factor protector de la demencia por enfermedad de Alzheimer. Rev Chil Ter Ocupacional. 2014;14(2):149-59. Disponible en: https://doi.org/10.5354/0719-5346.2014.35718

73.Gajardo J, Aravena JM. ¿Cómo aporta la terapia ocupacional en el tratamiento de las demencias? Rev Chil Neuro-Psiquiatr. 2016;54(3):239-49. Disponible en: https://doi.org/10.4067/S0717-92272016000300008

74.González MM, Rivera MM, García BF, Muñiz AL. Estilo de vida y riesgo de padecer demencia. Arch Med [Internet]. 2011 [citado el 8 de marzo de 2023];7(3):4–7. Disponible en: https://dialnet.unirioja.es/servlet/articulo?codigo=3708237

75.Borenstein AR, Wu Y, Mortimer JA, Schellenberg GD, McCormick WC, Bowen JD, et al. Developmental and vascular risk factors for Alzheimer's disease. Neurobiol Aging. 2005;26(3):325-34. Disponible en: https://doi.org/10.1016/j.neurobiolaging.2004.04.010

76.Reiss AB, Siller KA, Rahman MM, Chan ESL, Ghiso J, de Leon MJ. Cholesterol in neurologic disorders of the elderly: stroke and Alzheimer's disease. Neurobiol Aging. 1 de septiembre de 2004;25(8):977-89. Disponible en: https://doi.org/10.1016/j.neurobiolaging.2003.11.009

77.O'Brien JT, Markus HS. Vascular risk factors and Alzheimer's disease. BMC Med. 11 de noviembre de 2014;12(1):218. Disponible en: https://doi.org/10.1186/s12916-014-0218-y

78.Lyketsos CG, Olin J. Depression in Alzheimer's disease: overview and treatment. Biol Psychiatry. 1 de agosto de 2002;52(3):243-52. Disponible en: https://doi.org/10.1016/S0006-3223(02)01348-3

79.Starkstein SE, Mizrahi R. Depression in Alzheimer's disease. Expert Rev Neurother. 1 de junio de 2006;6(6):887-95. Disponible en: https://doi.org/10.1586/14737175.6.6.887

80.Kapogiannis D, Mustapic M, Shardell MD, Berkowitz ST, Diehl TC, Spangler RD, et al. Association of Extracellular Vesicle Biomarkers With Alzheimer Disease in the Baltimore Longitudinal Study of Aging. JAMA Neurol. 1 de noviembre de 2019;76(11):1340-51. Disponible en: https://doi.org/10.1001/jamaneurol.2019.2462

81.Wang C, Shou Y, Pan J, Du Y, Liu C, Wang H. The relationship between cholesterol level and Alzheimer's disease-associated APP proteolysis/Aβ metabolism. Nutr Neurosci. 3 de julio de 2019;22(7):453-63. Disponible en: https://doi.org/10.1080/1028415X.2017.1416942

82. Khachaturian ZS, Khachaturian AS. Politics of science: Progress toward prevention of the dementia-Alzheimer's syndrome. Mol Aspects Med. 1 de junio de 2015;43-44:3-15. Disponible en: https://doi.org/10.1016/j.mam.2015.06.001

83.Niu H, Álvarez-Álvarez I, Guillén-Grima F, Aguinaga-Ontoso I. Prevalencia e incidencia de la enfermedad de Alzheimer en Europa: metaanálisis. Neurología. 1 de octubre de 2017;32(8):523-32. Disponible en: https://doi.org/10.1016/j.nrl.2016.02.016

84.Cao Q, Tan CC, Xu W, Hu H, Cao XP, Dong Q, et al. The prevalence of dementia: a systematic review and meta-analysis. J Alzheimers Dis. 1 de enero de 2020;73(3):1157-66. Disponible en: https://doi.org/10.3233/JAD-191092

85.de Pedro-Cuesta J, Virués-Ortega J, Vega S, Seijo-Martínez M, Saz P, Rodríguez F, et al. Prevalence of dementia and major dementia subtypes in Spanish populations: A reanalysis of dementia prevalence surveys, 1990-2008. BMC Neurol. 19 de octubre de 2009;9(1):55. Disponible en: https://doi.org/10.1186/1471-2377-9-55

86.Alzheimer's Association. 2018 Alzheimer's disease facts and figures. Alzheimers Dement. 2018;14(3):367-429. Disponible en: https://doi.org/10.1016/j.jalz.2018.02.001

87.Lesser GT. Association of Alzheimer Disease Pathology with Abnormal Lipid Metabolism: The Hisayama Study. Neurology. 17 de abril de 2012;78(16):1280-1280. Disponible en: https://doi.org/10.1212/WNL.0b013e318254f6ad

88.Agirbasli M, Tanrikulu A, Acar Sevim B, Azizy M, Bekiroglu N. Total cholesterol-to-high-density lipoprotein cholesterol ratio predicts high-sensitivity C-reactive protein levels in Turkish children. J Clin Lipidol. 1 de marzo de 2015;9(2):195-200. Disponible en: https://doi.org/10.1016/j.jacl.2014.12.010

89.Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 25 de enero de 2005;64(2):277-81. Disponible en: https://doi.org/10.1212/01.WNL.0000149519.47454.F2

90.Versmissen J, Oosterveer DM, Blommesteijn-Touw AC, van Vark-van der Zee L, Vongpromek R, Mulder M, et al. Response to the letter by singh et al regarding "Apolipoprotein isoform e4 does not increase coronary heart disease risk in carriers of low-density lipoprotein receptor mutations". Circ Cardiovasc Genet. abril de 2012;5(2): e14-e14. Disponible en: https://doi.org/10.1161/CIRCGENETICS.111.962654

91.Nägga K, Gustavsson AM, Stomrud E, Lindqvist D, Westen D van, Blennow K, et al. Increased midlife triglycerides predict brain β-amyloid and tau pathology 20 years later. Neurology. 2 de enero de 2018;90(1): e73-81. Disponible en: https://doi.org/10.1212/WNL.0000000000004749

92.Hardy J. Alzheimer's disease: The amyloid cascade hypothesis: An update and reappraisal. J Alzheimers Dis. 1 de enero de 2006;9(s3):151-3. Disponible en: https://doi.org/10.3233/JAD-2006-9S317

93.Shibata N, Ohnuma T, Higashi S, Higashi M, Usui C, Ohkubo T, et al. No genetic association between PCSK9 polymorphisms and Alzheimer's disease and plasma cholesterol

level in Japanese patients. Psychiatr Genet. diciembre de 2005;15(4):239. Disponible en: https://doi.org/10.1097/00041444-200512000-00004

94.Michikawa M. Cholesterol paradox: Is high total or low HDL cholesterol level a risk for Alzheimer's disease? J Neurosci Res. 2003;72(2):141-6. Disponible en: https://doi.org/10.1002/jnr.10585

95.Wolf H, Hensel A, Arendt T, Kivipelto M, Winblad B, Gertz HJ. Association between serum HDL cholesterol and hippocampal volume. A link to Alzheimer's disease. Neurobiol Aging. 1 de julio de 2004;25: S52-3. Disponible en: https://doi.org/10.1016/S0197-4580(04)80178-7

96.Cleophas TJ, Zwinderman AH. Transforming Odds Ratios into Correlation Coefficients. En: Cleophas TJ, Zwinderman AH, editores. Modern Meta-Analysis: Review and Update of Methodologies [Internet]. Cham: Springer International Publishing; 2017 [citado 3 de diciembre de 2020]. p. 233-42. Disponible en: https://doi.org/10.1007/978-3-319-55895-0_20

97.Reis HT, Judd CM. Handbook of research methods in social and personality psychology. Cambridge University Press; 2000.

98.Shrier I, Steele R. Understanding the relationship between risks and odds ratios. Clin J Sport Med Off J Can Acad Sport Med. marzo de 2006;16(2):107-10. Disponible en: https://doi.org/10.1097/00042752-200603000-00004

99.Singh A, Hussain S, Najmi AK. Number of studies, heterogeneity, generalisability, and the choice of method for meta-analysis. J Neurol Sci. 15 de octubre de 2017; 381:347.

100. Disponible en: https://doi.org/10.1016/j.jns.2017.09.026

101. Borenstein M. Introduction to meta-analysis 2e. 2a ed. Hoboken, NJ, Estados Unidos de América: Wiley-Blackwell; 2021.

102. Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive meta-analysis (CMA) software. 2007;

103. Cohen J. Statistical power analysis for the behavioral sciences. Routledge; 2013.

104. Disponible en: https://doi.org/10.4324/9780203771587

105. Hall JR, Wiechmann AR, Johnson LA, Edwards M, Barber RC, Cunningham R, et al. Total Cholesterol and Neuropsychiatric Symptoms in Alzheimer's Disease: The Impact of Total Cholesterol Level and Gender. Dement Geriatr Cogn Disord. 2014;38(5-6):300-9. Disponible en: https://doi.org/10.1159/000361043

106. Reitz C, Tang MX, Luchsinger J, Mayeux R. Relation of plasma lipids to Alzheimer Disease and vascular dementia. Arch Neurol. 1 de mayo de 2004;61(5):705-14. Disponible en: Disponible en: https://doi.org/10.1001/archneur.61.5.705

107. Lauretti E, Praticò D. Alzheimer's disease: phenotypic approaches using disease models and the targeting of tau protein. Expert Opin Ther Targets. 2 de abril de 2020;24(4):319-30. Disponible en: https://doi.org/10.1080/14728222.2020.1737012

108. Theofilas P, Ehrenberg AJ, Nguy A, Thackrey JM, Dunlop S, Mejia MB, et al. Probing the correlation of neuronal loss, neurofibrillary tangles, and cell death markers across the Alzheimer's disease Braak stages: a quantitative study in humans. Neurobiol Aging. 1 de enero de 2018; 61:1-12. Disponible en: https://doi.org/10.1016/j.neurobiolaging.2017.09.007

109. Carleton RA, Dwyer J, Finberg L, Flora J, Goodman DS, Grundy SM, et al. Report of the expert panel on population strategies for blood cholesterol reduction. A statement from the National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health. Circulation. junio de 1991;83(6):2154-232. Disponible en: https://doi.org/10.1161/01.CIR.83.6.2154

110. Sharrett AR, Patsch W, Sorlie PD, Heiss G, Bond MG, Davis CE. Associations of lipoprotein cholesterols, apolipoproteins A-I and B, and triglycerides with carotid atherosclerosis and coronary heart disease. The Atherosclerosis Risk in Communities (ARIC)

Study. Arterioscler Thromb J Vasc Biol. julio de 1994;14(7):1098-104. Disponible en: https://doi.org/10.1161/01.ATV.14.7.1098

111. Breteler MMB, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam study. BMJ. 18 de junio de 1994;308(6944):1604-8. Disponible en: https://doi.org/10.1136/bmj.308.6944.1604

112. Tatemichi TK, Desmond DW, Prohovnik I, Eidelberg D. Dementia associated with bilateral carotid occlusions: neuropsychological and haemodynamic course after extracranial to intracranial bypass surgery. J Neurol Neurosurg Psychiatry. 1 de mayo de 1995;58(5):633-6. Disponible en: https://doi.org/10.1136/jnnp.58.5.633

113. Moroney JT, Tang MX, Berglund L, Small S, Merchant C, Bell K, et al. Low-density lipoprotein cholesterol and the risk of dementia with stroke. JAMA. 21 de julio de 1999;282(3):254-60. Disponible en: https://doi.org/10.1001/jama.282.3.254

114. Button EB, Robert J, Caffrey TM, Fan J, Zhao W, Wellington CL. HDL from an Alzheimer's disease perspective. Curr Opin Lipidol. junio de 2019;30(3):224-34. Disponible en: https://doi.org/10.1097/MOL.0000000000000604

115. Lepara O, Valjevac A, Alajbegović A, Zaćiragić A, Nakaš-Ićindić E. Decreased serum lipids in patients with probable Alzheimer's disease. Bosn J Basic Med Sci. agosto de 2009;9(3):215-20. Disponible en: https://doi.org/10.17305/bjbms.2009.2809

116. Reitz C, Tang MX, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Association of higher levels of high-density lipoprotein cholesterol in elderly individuals and lower risk of late-onset Alzheimer Disease. Arch Neurol. 1 de diciembre de 2010;67(12):1491-7. Disponible en: https://doi.org/10.1001/archneurol.2010.297

117. Wolozin B, Kellman W, Ruosseau P, Celesia GG, Siegel G. Decreased prevalence of Alzheimer Disease Associated with 3-hydroxy-3-methyglutaryl coenzyme a reductase inhibitors. Arch Neurol. 1 de octubre de 2000;57(10):1439-43. Disponible en: https://doi.org/10.1001/archneur.57.10.1439

118. Jick H, Zornberg G, Jick S, Seshadri S, Drachman D. Statins and the risk of dementia. The Lancet. 11 de noviembre de 2000;356(9242):1627-31. Disponible en: https://doi.org/10.1016/S0140-6736(00)03155-X

119. Reitz C, Luchsinger J, Tang MX, Manly J, Mayeux R. Impact of plasma lipids and time on memory performance in healthy elderly without dementia. Neurology. 26 de abril de 2005;64(8):1378-83. Disponible en: https://doi.org/10.1212/01.WNL.0000158274.31318.3C

120. Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. Bmj. 2001;322(7300):1447-51. Disponible en: https://doi.org/10.1136/bmj.322.7300.1447

121. Skoog I, Kalaria RN, Breteler MMB. Vascular Factors and Alzheimer Disease. Alzheimer Dis Assoc Disord. diciembre de 1999;13: S106. Disponible en: https://doi.org/10.1097/00002093-199912003-00016

122. An Y, Zhang X, Wang Y, Wang Y, Liu W, Wang T, et al. Longitudinal and nonlinear relations of dietary and Serum cholesterol in midlife with cognitive decline: results from EMCOA study. Mol Neurodegener. 30 de diciembre de 2019;14(1):51. Disponible en: https://doi.org/10.1186/s13024-019-0353-1

123. Clark LR, Norton D, Berman SE, Johnson SC, Bendlin BB, Wieben O, et al. Association of cardiovascular and Alzheimer's Disease risk factors with intracranial arterial blood flow in whites and African Americans. J Alzheimers Dis. 1 de enero de 2019;72(3):919-29. Disponible en: https://doi.org/10.3233/JAD-190645

124. Yanagisawa K. Cholesterol and pathological processes in Alzheimer's disease. J Neurosci Res. 2002;70(3):361-6. Disponible en: https://doi.org/10.1002/jnr.10348

125. Martínez DB, Soldevilla MG, Santiago AP, Martínez JT. Enfermedad de alzheimer. Med-Programa Form Médica Contin Acreditado. 2019;12(74):4338-46. Disponible en: https://doi.org/10.1016/j.med.2019.03.012

126. Huang LK, Chao SP, Hu CJ. Clinical trials of new drugs for Alzheimer disease. J Biomed Sci. 6 de enero de 2020;27(1):18. Disponible en: https://doi.org/10.1186/s12929-019-0609-7

127. de la Salud AM. Proyecto de plan de acción mundial sobre la respuesta de salud pública a la demencia: informe de la Directora General. Organización Mundial de la Salud; 2017. Disponible en: https://apps.who.int/iris/bitstream/handle/10665/273319/B140_28-sp.pdf?sequence=1&isAllowed=y

128. Niu H, Álvarez-Álvarez I, Guillén-Grima F, Aguinaga-Ontoso I. Prevalencia e incidencia de la enfermedad de Alzheimer en Europa: metaanálisis. Neurología. 1 de octubre de 2017;32(8):523-32. Disponible en: https://doi.org/10.1016/j.nrl.2016.02.016

129. Selkoe DJ. Alzheimer disease and aducanumab: adjusting our approach. Nat Rev Neurol. 2019;15(7):365-6. Disponible en: https://doi.org/10.1038/s41582-019-0205-1

130. Harris JR. Protein aggregation and fibrillogenesis in cerebral and systemic amyloid disease. Vol. 65. Springer Science & Business Media; 2012. Disponible en: https://doi.org/10.1007/978-94-007-5416-4

131. Dement A. Alzheimer's disease facts and figures. Alzheimer's Dement J Alzheimer's Assoc. 2016;12(4):459-509. Disponible en: https://doi.org/10.1016/j.jalz.2016.03.001

132. Migliaccio R, Agosta F, Rascovsky K, Karydas A, Bonasera S, Rabinovici GD, et al. Clinical syndromes associated with posterior atrophy: Early age at onset AD spectrum. Neurology. 10 de noviembre de 2009;73(19):1571-8. Disponible en: https://doi.org/10.1212/WNL.0b013e3181c0d427

133. Surguchov A. Caveolin: A new link between diabetes and ad. Cell Mol Neurobiol. 2020;1-8. Disponible en: https://doi.org/10.1007/s10571-020-00796-4

134. Tsuno N, Homma A. What is the association between depression and Alzheimer's disease? Expert Rev Neurother. 1 de noviembre de 2009;9(11):1667-76. Disponible en: https://doi.org/10.1586/ern.09.106

135. Depression W. Other common mental disorders: global health estimates. Geneva World Health Organ. 2017;1-24. Disponible en: https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf?s

136. Drevets WC, Rubin EH. Psychotic symptoms and the longitudinal course of senile dementia of the Alzheimer type. Biol Psychiatry. 1 de enero de 1989;25(1):39-48. Disponible en: https://doi.org/10.1016/0006-3223(89)90145-5

137. Lyketsos CG, Tune LE, Pearlson G, Steele C. Major Depression in Alzheimer's Disease: An Interaction Between Gender and Family History. Psychosomatics. 1 de julio de 1996;37(4):380-4. Disponible en: https://doi.org/10.1016/S0033-3182(96)71552-9

138. Oliveira FF de, Bertolucci PHF, Chen ES, Smith MC. Assessment of risk factors for earlier onset of sporadic Alzheimer's disease dementia. Neurol India. 11 de enero de 2014;62(6):625. Disponible en: https://doi.org/10.4103/0028-3886.149384

139. Cantón-Habas V, Rich-Ruiz M, Romero-Saldaña M, Carrera-González M del P. Depression as a risk factor for Dementia and Alzheimer's Disease. Biomedicines. noviembre de 2020;8(11):457. Disponible en: https://doi.org/10.3390/biomedicines8110457

140. Kuo CY, Stachiv I, Nikolai T. Association of Late Life Depression, (Non-) modifiable risk and protective factors with Dementia and Alzheimer's Disease: literature review on current evidences, preventive interventions and possible future trends in prevention and treatment of Dementia. Int J Environ Res Public Health. enero de 2020;17(20):7475. Disponible en: https://doi.org/10.3390/ijerph17207475

141. Gatz JL, Tyas SL, St. John P, Montgomery P. Do depressive symptoms predict Alzheimer's Disease and Dementia? J Gerontol Ser A. 1 de junio de 2005;60(6):744-7. Disponible en: https://doi.org/10.1093/gerona/60.6.744

142. Tapiainen V, Hartikainen S, Taipale H, Tiihonen J, Tolppanen AM. Hospital-treated mental and behavioral disorders and risk of Alzheimer's disease: A nationwide nested case-control study. Eur Psychiatry. 1 de junio de 2017; 43:92-8. Disponible en: https://doi.org/10.1016/j.eurpsy.2017.02.486

143. Becker JT, Chang YF, Lopez OL, Dew MA, Sweet RA, Barnes D, et al. Depressed mood is not a risk factor for incident dementia in a community-based cohort. Am J Geriatr Psychiatry. 2009;17(8):653-63. Disponible en: https://doi.org/10.1097/JGP.0b013e3181aad1fe

144. Hudon C, Escudier F, De Roy J, Croteau J, Cross N, Dang-Vu TT, et al. Behavioral and psychological symptoms that predict cognitive decline or impairment in cognitively normal middle-aged or older adults: a meta-analysis. Neuropsychol Rev. 2020; 30: 558-579. Disponible en: https://doi.org/10.1007/s11065-020-09437-5

145. Urrutia G, Bonfill X. PRISMA declaration: a proposal to improve the publication of systematic reviews and meta-analyses. Med Clínica. 2010;135(11):507-11. Disponible en: https://doi.org/10.1016/j.medcli.2010.01.015

146. Lipsey MW, Wilson DB. Practical meta-analysis. SAGE publications, Inc; 2001.

147. Bae JB, Kim YJ, Han JW, Kim TH, Park JH, Lee SB, et al. Incidence of and risk factors for Alzheimer's Disease and mild cognitive impairment in Korean elderly. Dement Geriatr Cogn Disord. 2015;39(1-2):105-15. Disponible en: https://doi.org/10.1159/000366555

148. Bartolini M, Coccia M, Luzzi S, Provinciali L, Ceravolo MG. Motivational symptoms of depression mask preclinical Alzheimer's Disease in elderly subjects. Dement Geriatr Cogn Disord. 2005;19(1):31-6. Disponible en: https://doi.org/10.1159/000080968

149. Blasko I, Kemmler G, Jungwirth S, Wichart I, Krampla W, Weissgram S, et al. Plasma amyloid beta-42 independently predicts both late-onset depression and Alzheimer Disease. Am J Geriatr Psychiatry. 1 de noviembre de 2010;18(11):973-82. Disponible en: https://doi.org/10.1097/JGP.0b013e3181df48be

150. Burke SL, Cadet T, Alcide A, O'Driscoll J, Maramaldi P. Psychosocial risk factors and Alzheimer's disease: the associative effect of depression, sleep disturbance, and anxiety. Aging Ment Health. 2 de diciembre de 2018;22(12):1577-84. Disponible en: https://doi.org/10.1080/13607863.2017.1387760

151. Chen P, Ganguli M, Mulsant BH, DeKosky ST. The temporal relationship between depressive symptoms and dementia: a community-based prospective study. Arch Gen Psychiatry. 1 de marzo de 1999;56(3):261-6. Disponible en: https://doi.org/10.1001/archpsyc.56.3.261

152. Dal Forno G, Palermo MT, Donohue JE, Karagiozis H, Zonderman AB, Kawas CH. Depressive symptoms, sex, and risk for Alzheimer's disease. Ann Neurol. 2005;57(3):381-7. Disponible en: https://doi.org/10.1002/ana.20405

153. Devanand DP, Sano M, Tang MX, Taylor S, Gurland BJ, Wilder D, et al. Depressed mood and the incidence of Alzheimer's Disease in the elderly living in the community. Arch Gen Psychiatry. 1 de febrero de 1996;53(2):175-82. Disponible en: https://doi.org/10.1001/archpsyc.1996.01830020093011

154. Dotson VM, Beydoun MA, Zonderman AB. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. Neurology. 6 de julio de 2010;75(1):27-34. Disponible en: https://doi.org/10.1212/WNL.0b013e3181e62124

155. Fuhrer R, Dufouil C, Dartigues JF, Study FTP. Exploring sex differences in the relationship between depressive symptoms and dementia incidence: prospective results from the PAQUID Study. J Am Geriatr Soc. 2003;51(8):1055-63. Disponible en: https://doi.org/10.1046/j.1532-5415.2003.51352.x

156. Geerlings MI, Bouter LM, Schoevers RA, Beekman ATF, Jonker C, Deeg DJH, et al. Depression and risk of cognitive decline and Alzheimer's disease: Results of two prospective community-based studies in the Netherlands. Br J Psychiatry. junio de 2000;176(6):568-75. Disponible en: https://doi.org/10.1192/bjp.176.6.568

157. Geerlings MI, Heijer T den, Koudstaal PJ, Hofman A, Breteler MMB. History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. Neurology. 8 de abril de 2008;70(15):1258-64. Disponible en: https://doi.org/10.1212/01.wnl.0000308937.30473.d1

158. Gracia-García P, de-la-Cámara C, Santabárbara J, Lopez-Anton R, Quintanilla MA, Ventura T, et al. Depression and incident Alzheimer Disease: the impact of disease severity. Am J Geriatr Psychiatry. 1 de febrero de 2015;23(2):119-29. Disponible en: https://doi.org/10.1016/j.jagp.2013.02.011

159. Heser K, Tebarth F, Wiese B, Eisele M, Bickel H, Köhler M, et al. Age of major depression onset, depressive symptoms, and risk for subsequent dementia: results of the German Study on Ageing, Cognition, and Dementia in Primary Care Patients (AgeCoDe). Psychol Med. agosto de 2013;43(8):1597-610. Disponible en: https://doi.org/10.1017/S0033291712002449

160. Irie F, Masaki KH, Petrovitch H, Abbott RD, Ross GW, Taaffe DR, et al. Apolipoprotein E ε4 allele genotype and the effect of depressive symptoms on the risk of dementia in men: the honolulu-Asia aging study. Arch Gen Psychiatry. 4 de agosto de 2008;65(8):906-12. Disponible en: https://doi.org/10.1001/archpsyc.65.8.906

161. Kim JM, Kim SY, Bae KY, Kim SW, Shin IS, Yang SJ, et al. Apolipoprotein E4 genotype and depressive symptoms as risk factors for dementia in an older Korean population. Psychiatry Investig. junio de 2010;7(2):135-40. Disponible en: https://doi.org/10.4306/pi.2010.7.2.135

162. Kim JM, Stewart R, Kim SY, Kim SW, Bae KY, Yang SJ, et al. Synergistic associations of depression and apolipoprotein E genotype with incidence of dementia. Int J Geriatr Psychiatry. 2011;26(9):893-8. Disponible en: https://doi.org/10.1002/gps.2621

163. Lauriola M, Mangiacotti A, D'Onofrio G, Cascavilla L, Paris F, Ciccone F, et al. Late-Life Depression versus amnestic mild cognitive impairment: Alzheimer's Disease incidence in 4 years of follow-up. Dement Geriatr Cogn Disord. 2018;46(3-4):140-53. Disponible en: https://doi.org/10.1159/000492489

164. Lenoir H, Dufouil C, Auriacombe S, Lacombe JM, Dartigues JF, Ritchie K, et al. Depression history, depressive symptoms, and incident dementia: The 3C Study. J Alzheimers Dis. 1 de enero de 2011;26(1):27-38. Disponible en: https://doi.org/10.3233/JAD-2011-101614

165. Li G, Wang LY, Shofer JB, Thompson ML, Peskind ER, McCormick W, et al. Temporal Relationship Between Depression and Dementia: Findings From a Large Community-Based 15-Year Follow-up Study. Arch Gen Psychiatry. 1 de septiembre de 2011;68(9):970-7. Disponible en: https://doi.org/10.1001/archgenpsychiatry.2011.86

166. Luchsinger J, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. Neurology. 2005;65(4):545-51. Disponible en: https://doi.org/10.1212/01.wnl.0000172914.08967.dc

167. Reding M, Haycox J, Blass J. Depression in patients referred to a dementia clinic: a three-year prospective study. Arch Neurol. 1 de septiembre de 1985;42(9):894-6. Disponible en: https://doi.org/10.1001/archneur.1985.04060080080019

168. Richard E, Reitz C, Honig LH, Schupf N, Tang MX, Manly JJ, et al. Late-life depression, mild cognitive impairment, and Dementia. JAMA Neurol. 1 de marzo de 2013;70(3):383-9. Disponible en: https://doi.org/10.1001/jamaneurol.2013.603

169. Saczynski JS, Beiser A, Seshadri S, Auerbach S, Wolf PA, Au R. Depressive symptoms and risk of dementia: The Framingham Heart Study. Neurology. 6 de julio de 2010;75(1):35-41. Disponible en: https://doi.org/10.1212/WNL.0b013e3181e62138

170. Tyas SL, Manfreda J, Strain LA, Montgomery PR. Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. Int J Epidemiol. 2001;30(3):590-7. Disponible en: https://doi.org/10.1093/ije/30.3.590

171. Vilalta-Franch J, López-Pousa S, Llinàs-Reglà J, Calvó-Perxas L, Merino-Aguado J, Garre-Olmo J. Depression subtypes and 5-year risk of dementia and Alzheimer disease in patients aged 70 years. Int J Geriatr Psychiatry. 2013;28(4):341-50. Disponible en: https://doi.org/10.1002/gps.3826

172. Wilson RS, Schneider JA, Bienias JL, Arnold SE, Evans DA, Bennett DA. Depressive symptoms, clinical AD, and cortical plaques and tangles in older persons. Neurology. 28 de octubre de 2003;61(8):1102-7. Disponible en: https://doi.org/10.1212/01.WNL.0000092914.04345.97

173. Kuring JK, Mathias JL, Ward L. Prevalence of depression, anxiety and PTSD in people with Dementia: a systematic review and meta-analysis. Neuropsychol Rev. 1 de diciembre de 2018;28(4):393-416. Disponible en: https://doi.org/10.1007/s11065-018-9396-2

174. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol. 1967;6(4):278-96. Disponible en: https://doi.org/10.1111/j.2044-8260.1967.tb00530.x

175. Williams JBW. A structured interview guide for the Hamilton Depression rating scale. Arch Gen Psychiatry. 1 de agosto de 1988;45(8):742-7. Disponible en: https://doi.org/10.1001/archpsyc.1988.01800320058007

176. Copeland JRM, Dewey ME, Griffiths-Jones HM. A computerized psychiatric diagnostic system and case nomenclature for elderly subjects: GMS and AGECAT. Psychol Med. febrero de 1986;16(1):89-99. Disponible en: https://doi.org/10.1017/S0033291700057779

177. Jung I-K, Kwak D-I, Sook-Haeng JOE, Hyeon-Soo LEE. A study of standardization of Korean form of geriatric depression scale(KGDS). Journal of Korean Geriatric Psychiatry [Internet]. 1997 [citado el 8 de marzo de 2023];61–72. Disponible en: https://pesquisa.bvsalud.org/portal/resource/pt/wpr-21181

178. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res. 1 de enero de 1982;17(1):37-49. Disponible en: https://doi.org/10.1016/0022-3956(82)90033-4

179. Kim JY, Park JH, Lee JJ, Huh Y, Lee SB, Han SK, et al. Standardization of the Korean version of the Geriatric Depression Scale: Reliability, Validity, and Factor Structure. Psychiatry Investig. diciembre de 2008;5(4):232-8. Disponible en: https://doi.org/10.4306/pi.2008.5.4.232

180. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl Psychol Meas. 1 de junio de 1977;1(3):385-401. Disponible en: https://doi.org/10.1177/014662167700100306

181. Kohout FJ, Berkman LF, Evans DA, Cornoni-Huntley J. Two shorter forms of the CES-D Depression symptoms index. J Aging Health. 1 de mayo de 1993;5(2):179-93. Disponible en: https://doi.org/10.1177/089826439300500202

182. Reis HT, Judd CM. Handbook of Research Methods in Social and Personality Psychology. Cambridge University Press; 2000. 574 p.

183. Henderson AS, Korten AE, Jacomb PA, Mackinnon AJ, Jorm AF, Christensen H, et al. The course of depression in the elderly: a longitudinal community-based study in Australia. Psychol Med. enero de 1997;27(1):119-29. Disponible en: https://doi.org/10.1017/S0033291796004199

184. Class CA, Unverzagt FW, Gao S, Sahota A, Hall KS, Hendrie HC. The association between Apo E genotype and depressive symptoms in elderly African-American Subjects.

Am J Geriatr Psychiatry. 1 de septiembre de 1997;5(4):339-43. Disponible en: https://doi.org/10.1097/00019442-199700540-00009

185. Forsell Y, Corder EH, Basun H, Lannfelt L, Viitanen M, Winblad B. Depression and dementia in relation to apolipoprotein E polymorphism in a population sample age 75+. Biol Psychiatry. 15 de noviembre de 1997;42(10):898-903. Disponible en: https://doi.org/10.1016/S0006-3223(96)00468-4

186. Zubenko GS, Henderson R, Scott Stiffler J, Stabler S, Rosen J, Kaplan BB. Association of the APOE ε4 allele with clinical subtypes of late life depression. Biol Psychiatry. 15 de noviembre de 1996;40(10):1008-16. Disponible en: https://doi.org/10.1016/S0006-3223(96)00046-7

187. Puy L, Jouvent E. Accidente cerebrovascular en el paciente anciano. EMC - Tratado Med. 1 de marzo de 2020;24(1):1-6. Disponible en: https://doi.org/10.1016/S1636-5410(20)43329-X

188. Ouanes S, Popp J. High cortisol and the risk of dementia and Alzheimer's disease: A review of the literature. Front Aging Neurosci [Internet]. 2019; 11:43. Disponible en: http://dx.doi.org/10.3389/fnagi.2019.00043

189. Hong H, Kim BS, Im HI. Pathophysiological Role of neuroinflammation in neurodegenerative diseases and psychiatric disorders. Int Neurourol J. mayo de 2016;20(Suppl 1): S2-7. Disponible en: https://doi.org/10.5213/inj.1632604.302

190. Han HF, Yen HC, Wu HC, Tan HY, Xu W, Jiang HS, et al. Ultrasensitive detection of Alzheimer's amyloids on a plasmonic-gold platform. ACS Appl Mater Interfaces. 2021; Disponible en: https://doi.org/10.1021/acsami.1c19157

191. Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues Clin Neurosci. 30 de junio de 2009;11(2):111-28. Disponible en: https://doi.org/10.31887/DCNS.2009.11.2/cqiu

192. Bhushan I, Kour M, Kour G, Gupta S, Sharma S, Yadav A. Alzheimer's disease: Causes and treatment-A review. Ann Biotechnol. 2018;1(1):1002. Disponible en: https://doi.org/10.33582/2637-4927/1002

193. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement. 2007;3(3):186-91. Disponible en: https://doi.org/10.1016/j.jalz.2007.04.381

194. Satizabal CL, Beiser AS, Chouraki V, Chêne G, Dufouil C, Seshadri S. Incidence of dementia over three decades in the Framingham Heart Study. N Engl J Med. 2016;374(6):523-32. Disponible en: https://doi.org/10.1056/NEJMoa1504327

195. Gottesman RT, Stern Y. Behavioral and psychiatric symptoms of dementia and rate of decline in Alzheimer's disease. Front Pharmacol. 2019; 10:1062. Disponible en: https://doi.org/10.3389/fphar.2019.01062

196. C. Vickers J, Mitew S, Woodhouse A, M. Fernandez-Martos C, T. Kirkcaldie M, J. Canty A, et al. Defining the earliest pathological changes of Alzheimer's disease. Curr Alzheimer Res. 1 de marzo de 2016;13(3):281-7. Disponible en: https://doi.org/10.2174/1567205013666151218150322

197. Reisberg B, Jamil IA, Khan S, Monteiro I, Torossian C, Ferris S, et al. Staging dementia. Princ Pract Geriatr Psychiatry. 2010;162-9. Disponible en: https://doi.org/10.1002/9780470669600.ch31

198. Association AP. DSM-5: Manual diagnóstico y estadístico de los trastornos mentales. 2014;

199. Groves WC, Brandt J, Steinberg M, Warren A, Rosenblatt A, Baker A, et al. Vascular Dementia and Alzheimer's Disease: Is there a difference? J Neuropsychiatry Clin Neurosci. agosto de 2000;12(3):305-15. Disponible en: https://doi.org/10.1176/jnp.12.3.305

200. Epperly TD, Dunay MA, Boice JL. Alzheimer disease: pharmacologic and nonpharmacologic therapies for cognitive and functional symptoms. Am Fam Physician.

2017;95(12):771-8. Disponible en: https://www.aafp.org/pubs/afp/issues/2017/0615/p771.html

201. Orona CJ. Temporality and identity loss due to Alzheimer's disease. Soc Sci Med. 1990;30(11):1247-56. Disponible en: https://doi.org/10.1016/0277-9536(90)90265-T

202. Guarino A, Favieri F, Boncompagni I, Agostini F, Cantone M, Casagrande M. Executive functions in Alzheimer disease: a systematic review. Front Aging Neurosci. 2019; 10:437. Disponible en: https://doi.org/10.3389/fnagi.2018.00437

203. Deutsch LH, Bylsma FW, Rovner BW, Steele C, Folstein MF. Psychosis and physical aggression in probable Alzheimer's disease. Am J Psychiatry [Internet]. 1991;148(9):1159–63. Disponible en: https://psycnet.apa.org/fulltext/1992-02181-001.pdf

204. Giebel CM, Sutcliffe C, Challis D. Activities of daily living and quality of life across different stages of dementia: a UK study. Aging Ment Health. 2015;19(1):63-71. Disponible en: https://doi.org/10.1080/13607863.2014.915920

205. Castelli WP, Wilson PWF, Levy D, Anderson K. Cardiovascular risk factors in the elderly. Am J Cardiol. 2 de mayo de 1989;63(16):12-9. Disponible en: https://doi.org/10.1016/0002-9149(89)90110-0

206. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Enfermedad de Alzheimer. The Lancet. 2011;377(9770):1019-31. Disponible en: https://doi.org/10.1016/S0140-6736(10)61349-9

207. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005;4(8):487-99. Disponible en: https://doi.org/10.1016/S1474-4422(05)70141-1

208. Marfany A, Sierra C, Camafort M, Domenech M, Coca A. High blood pressure, Alzheimer disease and antihypertensive treatment. Panminerva Med. 2018;60(1):8-16. Disponible en: https://doi.org/10.23736/S0031-0808.18.03360-8

209. Silva JA da. Caracterização das abordagens farmacológicas usadas no tratamento das demências-análise de casos do CHCB. 2014.

210. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study☆. Neurobiol Aging. 2000;21(1):49-55. Disponible en: https://doi.org/10.1016/S0197-4580(00)00096-8

211. Posner HB, Tang MX, Luchsinger J, Lantigua R, Stern Y, Mayeux R. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. Neurology. 2002;58(8):1175-81. Disponible en: https://doi.org/10.1212/WNL.58.8.1175

212. Morris MC, Scherr PA, Hebert LE, Glynn RJ, Bennett DA, Evans DA. Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. Arch Neurol. 2001;58(10):1640-6. Disponible en: https://doi.org/10.1001/archneur.58.10.1640

213. Miyoshi K. What is 'early onset dementia'? Psychogeriatrics. 2009;9(2):67-72. Disponible en: https://doi.org/10.1111/j.1479-8301.2009.00274.x

214. Guo Z, Viitanen M, Fratiglioni L, Winblad B. Low blood pressure and dementia in elderly people: the Kungsholmen project. BMJ. 30 de marzo de 1996;312(7034):805-8. Disponible en: https://doi.org/10.1136/bmj.312.7034.805

215. Euser SM, Van Bemmel T, Schram MT, Gussekloo J, Hofman A, Westendorp RG, et al. The effect of age on the association between blood pressure and cognitive function later in life. J Am Geriatr Soc. 2009;57(7):1232-7. Disponible en: https://doi.org/10.1111/j.1532-5415.2009.02264.x

216. Gillis EE, Sullivan JC. Sex differences in hypertension: recent advances. Hypertension. 2016;68(6):1322-7. Disponible en: https://doi.org/10.1161/HYPERTENSIONAHA.116.06602

217. Anstey KJ, Peters R, Mortby ME, Kiely KM, Eramudugolla R, Cherbuin N, et al. Association of sex differences in dementia risk factors with sex differences in memory

decline in a population-based cohort spanning 20-76 years. Sci Rep. 8 de abril de 2021;11(1):7710. Disponible en: https://doi.org/10.1038/s41598-021-86397-7

218. Ramirez LA, Sullivan JC. Sex differences in hypertension: where we have been and where we are going. Am J Hypertens. 2018;31(12):1247-54. Disponible en: https://doi.org/10.1093/ajh/hpy148

219. Zhou B, Danaei G, Stevens GA, Bixby H, Taddei C, Carrillo-Larco RM, et al. Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. The Lancet. 2019;394(10199):639-51. Disponible en: https://doi.org/10.1016/S0140-6736(19)31145-6

220. Mills KT, Obst KM, Shen W, Molina S, Zhang HJ, He H, et al. Comparative effectiveness of implementation strategies for blood pressure control in hypertensive patients: a systematic review and meta-analysis. Ann Intern Med. 2018;168(2):110-20. Disponible en: https://doi.org/10.7326/M17-1805

221. Tibazarwa KB, Damasceno AA. Hypertension in developing countries. Can J Cardiol. 2014;30(5):527-33. Disponible en: https://doi.org/10.1016/j.cjca.2014.02.020

222. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International society of hypertension global hypertension practice guidelines. Hypertension. junio de 2020;75(6):1334-57. Disponible en: https://doi.org/10.1161/HYPERTENSIONAHA.120.15026

223. Stergiou GS, Parati G, McManus RJ, Head GA, Myers MG, Whelton PK. Guidelines for blood pressure measurement: development over 30 years. J Clin Hypertens. 2018;20(7):1089-91. Disponible en: https://doi.org/10.1111/jch.13295

224. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. Clin Epidemiol. 2014; 6:37. Disponible en: https://doi.org/10.2147/CLEP.S37929

225. Prins N, Den Heijer T, Hofman A, Koudstaal P, Jolles J, Clarke R, et al. Homocysteine and cognitive function in the elderly: the Rotterdam Scan Study. Neurology. 2002;59(9):1375-80. Disponible en: https://doi.org/10.1212/01.WNL.0000032494.05619.93

226. Nutaitis AC, Tharwani SD, Serra MC, Goldstein FC, Zhao L, Sher SS, et al. Diet as a risk factor for cognitive decline in African Americans and caucasians with a parental history of Alzheimer's Disease: A Cross-Sectional Pilot Study Dietary Patterns. J Prev Alzheimers Dis. 1 de enero de 2019;6(1):50-5. Disponible en: https://doi.org/10.14283/jpad.2018.44

227. Lesener T, Gusy B, Wolter C. The job demands-resources model: A meta-analytic review of longitudinal studies. Work Stress. 2019;33(1):76-103. Disponible en: https://doi.org/10.1080/02678373.2018.1529065

228. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34(7):939-939. Disponible en: https://doi.org/10.1212/WNL.34.7.939

229. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 13 de septiembre de 1997;315(7109):629-34. Disponible en: https://doi.org/10.1136/bmj.315.7109.629

230. McGrath ER, Beiser AS, DeCarli C, Plourde KL, Vasan RS, Greenberg SM, et al. Blood pressure from mid-to late life and risk of incident dementia. Neurology. 2017;89(24):2447-54. Disponible en: https://doi.org/10.1212/WNL.0000000000004741

231. Chiang CJ, Yip PK, Wu SC, Lu CS, Liou CW, Liu HC, et al. Midlife risk factors for subtypes of dementia: a nested case-control study in Taiwan. Am J Geriatr Psychiatry. 2007;15(9):762-71. Disponible en: https://doi.org/10.1097/JGP.0b013e318050c98f

232. Kimm H, Lee P, Shin Y, Park K, Jo J, Lee Y, et al. Mid-life and late-life vascular risk factors and dementia in Korean men and women. Arch Gerontol Geriatr. 2011;52(3): e117-22. Disponible en: https://doi.org/10.1016/j.archger.2010.09.004

233. Ninomiya T, Ohara T, Hirakawa Y, Yoshida D, Doi Y, Hata J, et al. Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama study. Hypertension. 2011;58(1):22-8. Disponible en: https://doi.org/10.1161/HYPERTENSIONAHA.110.163055

234. Verghese J, Lipton R, Hall C, Kuslansky G, Katz M. Low blood pressure and the risk of dementia in very old individuals. Neurology. 2003;61(12):1667-72. Disponible en: https://doi.org/10.1212/01.WNL.0000098934.18300.BE

235. Bermejo-Pareja F, Benito-León J, Louis ED, Trincado R, Carro E, Villarejo A, et al. Risk of incident dementia in drug-untreated arterial hypertension: a population-based study. J Alzheimers Dis. 2010;22(3):949-58. Disponible en: https://doi.org/10.3233/JAD-2010-101110

236. Huang CC, Chung CM, Leu HB, Lin LY, Chiu CC, Hsu CY, et al. Diabetes mellitus and the risk of Alzheimer's disease: a nationwide population-based study. PloS One. 2014;9(1): e87095. Disponible en: https://doi.org/10.1371/journal.pone.0087095

237. Chu LW, Tam S, Wong RL, Yik PY, Song Y, Cheung BM, et al. Bioavailable testosterone predicts a lower risk of Alzheimer's disease in older men. J Alzheimers Dis. 2010;21(4):1335-45. Disponible en: https://doi.org/10.3233/JAD-2010-100027

238. Forti P, Pisacane N, Rietti E, Lucicesare A, Olivelli V, Mariani E, et al. Metabolic syndrome and risk of dementia in older adults. J Am Geriatr Soc. 2010;58(3):487-92. Disponible en: https://doi.org/10.1111/j.1532-5415.2010.02731.x

239. Song X, Mitnitski A, Rockwood K. Nontraditional risk factors combine to predict Alzheimer disease and dementia. Neurology. 2011;77(3):227-34. Disponible en: https://doi.org/10.1212/WNL.0b013e318225c6bc

240. Raffaitin C, Gin H, Empana JP, Helmer C, Berr C, Tzourio C, et al. Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: the Three-City Study. Diabetes Care. 2009;32(1):169-74. Disponible en: https://doi.org/10.2337/dc08-0272

241. Muller M, Tang MX, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Metabolic syndrome and dementia risk in a multiethnic elderly cohort. Dement Geriatr Cogn Disord. 2007;24(3):185-92. Disponible en: https://doi.org/10.1159/000105927

242. Lindsay J, Laurin D, Verreault R, Hébert R, Helliwell B, Hill GB, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol. 2002;156(5):445-53. Disponible en: https://doi.org/10.1093/aje/kwf074

243. Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, et al. Apolipoprotein E ε4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med. 2002;137(3):149-55. Disponible en: https://doi.org/10.7326/0003-4819-137-3-200208060-00006

244. Hayden KM, Zandi PP, Lyketsos CG, Khachaturian AS, Bastian LA, Charoonruk G, et al. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. Alzheimer Dis Assoc Disord. 2006;20(2):93-100. Disponible en: https://doi.org/10.1097/01.wad.0000213814.43047.86

245. Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, et al. Risk factors for dementia in the cardiovascular health cognition study. Neuroepidemiology. 2003;22(1):13-22. Disponible en: https://doi.org/10.1159/000067109

246. Rönnemaa E, Zethelius B, Lannfelt L, Kilander L. Vascular risk factors and dementia: 40-year follow-up of a population-based cohort. Dement Geriatr Cogn Disord. 2011;31(6):460-6. Disponible en: https://doi.org/10.1159/000330020

247. Annweiler C, Rolland Y, Schott AM, Blain H, Vellas B, Herrmann FR, et al. Higher vitamin D dietary intake is associated with lower risk of Alzheimer's disease: a 7-year follow-up. J Gerontol Ser Biomed Sci Med Sci. 2012;67(11):1205-11. Disponible en: https://doi.org/10.1093/gerona/gls107

248. Wang KC, Woung LC, Tsai MT, Liu CC, Su YH, Li CY. Risk of Alzheimer's disease in relation to diabetes: a population-based cohort study. Neuroepidemiology. 2012;38(4):237-44. Disponible en: https://doi.org/10.1159/000337428

249. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. Arch Intern Med. 2006;166(9):1003-8. Disponible en: https://doi.org/10.1001/archinte.166.9.1003

250. Olazarán J, Trincado R, Bermejo-Pareja F. Cumulative effect of depression on dementia risk. Int J Alzheimers Dis [Internet]. 2013 [citado el 8 de marzo de 2023]; 2013:457175. Disponible en: https://www.hindawi.com/journals/ijad/2013/457175/

251. Harwood DG, Barker WW, Loewenstein DA, Ownby RL, George-Hyslop PS, Mullan M, et al. A cross-ethnic analysis of risk factors for AD in white Hispanics and white non-Hispanics. Neurology. 1999;52(3):551-551. Disponible en: https://doi.org/10.1212/WNL.52.3.551

252. Wu C, Zhou D, Wen C, Zhang L, Como P, Qiao Y. Relationship between blood pressure and Alzheimer's disease in Linxian County, China. Life Sci. 2003;72(10):1125-33. Disponible en: https://doi.org/10.1016/S0024-3205(02)02367-6

253. Brayne C, Gill C, Huppert FA, Barkley C, Gehlhaar E, Girling DM, et al. Vascular risks and incident dementia: results from a cohort study of the very old. Dement Geriatr Cogn Disord. 1998;9(3):175-80. Disponible en: https://doi.org/10.1159/000017043

254. Mendez MF, Underwood KL, Zander BA, Mastri AR, Sung JH, Frey WH. Risk factors in Alzheimer's disease: a clinicopathologic study. Neurology. 1992;42(4):770-770. Disponible en: https://doi.org/10.1212/WNL.42.4.770

255. French LR, Schuman LM, Mortimer JA, Hutton JT, Boatman RA, Christians B. A case-control study of dementia of the Alzheimer type. Am J Epidemiol. 1985;121(3):414-21. Disponible en: https://doi.org/10.1093/oxfordjournals.aje.a114013

256. Kokmen E, Beard CM, Chandra V, Offord KP, Schoenberg BS, Ballard DJ. Clinical risk factors for Alzheimer's disease: a population-based case-control study. Neurology. 1991;41(9):1393-1393. Disponible en: https://doi.org/10.1212/WNL.41.9.1393

257. Foroughan M, Farahani ZG, Shariatpanahi M, Vaezinejad M, Akbari Kamerani AA, Sheikhvatan M. Risk factors of Alzheimer's disease among Iranian population. Curr Alzheimer Res. 2008;5(1):70-2. Disponible en: https://doi.org/10.2174/156720508783884594

258. Roberts RO, Cha RH, Knopman DS, Petersen RC, Rocca WA. Postmenopausal estrogen therapy and Alzheimer disease: overall negative findings. Alzheimer Dis Assoc Disord. 2006;20(3):141-6. Disponible en: https://doi.org/10.1097/00002093-200607000-00004

259. Kubis-Kubiak A, Rorbach-Dolata A, Piwowar A. Crucial players in Alzheimer's disease and diabetes mellitus: Friends or foes? Mech Ageing Dev. 2019; 181:7-21. Disponible en: https://doi.org/10.1016/j.mad.2019.03.008

260. Suhanov AV, Pilipenko PI, Korczyn AD, Hofman A, Voevoda MI, Shishkin SV, et al. Risk factors for Alzheimer's disease in Russia: a case-control study. Eur J Neurol. 2006;13(9):990-5. Disponible en: https://doi.org/10.1111/j.1468-1331.2006.01391.x

261. Graves AB, White E, Koepsell TD, Reifler BV, Van Belle G, Larson EB, et al. A case-control study of Alzheimer's disease. Ann Neurol Off J Am Neurol Assoc Child Neurol Soc. 1990;28(6):766-74. Disponible en: https://doi.org/10.1002/ana.410280607

262. Tsolaki M, Fountoulakis K, Chantzi E, Kazis A. Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of a Greek population. Int Psychogeriatr. 1997;9(3):327-41. Disponible en: https://doi.org/10.1017/S104161029700447X

263. Imfeld P, Bodmer M, Jick SS, Meier CR. Metformin, other antidiabetic drugs, and risk of Alzheimer's disease: a population-based case-control study. J Am Geriatr Soc. 2012;60(5):916-21. Disponible en: https://doi.org/10.1111/j.1532-5415.2012.03916.x

264. Hurtado JC, Salazar T, de la Peña M. Valores normales de gases arteriales en Bogotá. Bogotá Colomb. junio de 2007; 10:93-101. Disponible en: https://dialnet.unirioja.es/descarga/articulo/2387855.pdf

265. Qiu C, Xu W, Winblad B, Fratiglioni L. Vascular risk profiles for dementia and Alzheimer's disease in very old people: a population-based longitudinal study. J Alzheimers Dis. 2010;20(1):293-300. Disponible en: https://doi.org/10.3233/JAD-2010-1361

266. Li G, Rhew IC, Shofer JB, Kukull WA, Breitner JC, Peskind E, et al. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study. J Am Geriatr Soc. 2007;55(8):1161-7. Disponible en: https://doi.org/10.1111/j.1532-5415.2007.01233.x

267. Ruitenberg A, Skoog I, Ott A, Aevarsson O, Witteman JC, Lernfelt B, et al. Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. Dement Geriatr Cogn Disord. 2001;12(1):33-9. Disponible en: https://doi.org/10.1159/000051233

268. Shah RC, Wilson RS, Bienias JL, Arvanitakis Z, Evans DA, Bennett DA. Relation of blood pressure to risk of incident Alzheimer's disease and change in global cognitive function in older persons. Neuroepidemiology. 2006;26(1):30-6. Disponible en: https://doi.org/10.1159/000089235

269. Stewart R, Xue QL, Masaki K, Petrovitch H, Ross GW, White LR, et al. Change in blood pressure and incident dementia: a 32-year prospective study. Hypertension. 2009;54(2):233-40. Disponible en: https://doi.org/10.1161/HYPERTENSIONAHA.109.128744

270. Treiber KA, Lyketsos CG, Corcoran C, Steinberg M, Norton M, Green RC, et al. Vascular factors and risk for neuropsychiatric symptoms in Alzheimer's disease: the Cache County Study. Int Psychogeriatr. 2008;20(3):538-53. Disponible en: https://doi.org/10.1017/S1041610208006704

271. Hassing LB, Dahl AK, Thorvaldsson V, Berg S, Gatz M, Pedersen NL, et al. Overweight in midlife and risk of dementia: a 40-year follow-up study. Int J Obes. 2009;33(8):893-8. Disponible en: https://doi.org/10.1038/ijo.2009.104

272. Tini G, Scagliola R, Monacelli F, La Malfa G, Porto I, Brunelli C, et al. Alzheimer's disease and cardiovascular disease: A particular association. Cardiol Res Pract [Internet]. 2020 [citado el 8 de marzo de 2023]; 2020:2617970. Disponible en: https://www.hindawi.com/journals/crp/2020/2617970/

273. Sparks DL, Scheff SW, Liu H, Landers TM, Coyne CM, Hunsaker III JC. Increased incidence of neurofibrillary tangles (NFT) in non-demented individuals with hypertension. J Neurol Sci. 1995;131(2):162-9. Disponible en: https://doi.org/10.1016/0022-510X(95)00105-B

274. Murphy SJ, Werring DJ. Stroke: causes and clinical features. Medicine (Baltimore). 2020; 48(9):561-566. Disponible en: https://doi.org/10.1016/j.mpmed.2020.06.002

275. Hachinski V, Einhäupl K, Ganten D, Alladi S, Brayne C, Stephan BC, et al. Preventing dementia by preventing stroke: the Berlin Manifesto. Alzheimers Dement. 2019;15(7):961-84. Disponible en: https://doi.org/10.1016/j.jalz.2019.06.001

276. Loera-Valencia R, Cedazo-Minguez A, Kenigsberg P, Page G, Duarte A, Giusti P, et al. Current and emerging avenues for Alzheimer's disease drug targets. J Intern Med. 2019;286(4):398-437. Disponible en: https://doi.org/10.1111/joim.12959

277. Kuljiš RO, Šalković-Petrišić M. Dementia, diabetes, Alzheimer's disease, and insulin resistance in the brain: progress, dilemmas, new opportunities, and a hypothesis to tackle intersecting epidemics. J Alzheimers Dis. 2011;25(1):29-41. Disponible en: https://doi.org/10.3233/JAD-2011-101392

278. Ponce-López T, Sorsby-Vargas AM, Bocanegra-López AP, Luna-Muñoz J, Ontiveros-Torres MA, Villanueva-Fierro I, et al. Diabetes mellitus and amyloid beta protein pathology

in dementia. En: Amyloid Diseases. IntechOpen; 2019. Disponible en: https://doi.org/10.5772/intechopen.84473

279. Nelson L, Gard P, Tabet N. Hypertension and inflammation in Alzheimer's disease: close partners in disease development and progression. J Alzheimers Dis. 2014;41(2):331-43. Disponible en: https://doi.org/10.3233/JAD-140024

280. Skoog I, Gustafson D. Update on hypertension and Alzheimer's disease. Neurol Res. 2006;28(6):605-11. Disponible en: https://doi.org/10.1179/016164106X130506

281. Benetos A, Thomas F, Safar ME, Bean KE, Guize L. Should diastolic and systolic blood pressure be considered for cardiovascular risk evaluation: a study in middle-aged men and women. J Am Coll Cardiol. enero de 2001;37(1):163-8. Disponible en: https://doi.org/10.1016/S0735-1097(00)01092-5

282. Katayama T, Hasebe N. Angiotensin-Receptor Blockers, Hypertension and Alzheimer Disease-The Entangled Relationship-. Circ J. 2013;77(2):315-6. Disponible en: https://doi.org/10.1253/circj.CJ-12-1550

283. Iadecola C. Hypertension and dementia. Hypertension. 2014;64(1):3-5. Disponible en: https://doi.org/10.1161/HYPERTENSIONAHA.114.03040

284. World Bank. World bank country and lending groups 2020. 2020;

285. Zhou B, Lu Y, Hajifathalian K, Bentham J, Di Cesare M, Danaei G, et al. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. The Lancet. 2016;387(10027):1513-30. Disponible en: https://doi.org/10.1016/S0140-6736(16)00618-8

286. Turana Y, Tengkawan J, Chia YC, Hoshide S, Shin J, Chen CH, et al. Hypertension and Dementia: A comprehensive review from the HOPE Asia Network. J Clin Hypertens. 2019;21(8):1091-8. Disponible en: https://doi.org/10.1111/jch.13558

287. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global Disparities of Hypertension Prevalence and Control. Circulation. 9 de agosto de

2016;134(6):441-50. Disponible en: https://doi.org/10.1161/CIRCULATIONAHA.115.018912

288. Piff PK, Stancato DM, Côté S, Mendoza-Denton R, Keltner D. Higher social class predicts increased unethical behavior. Proc Natl Acad Sci. 13 de marzo de 2012;109(11):4086-91. Disponible en: https://doi.org/10.1073/pnas.1118373109

289. Barker WW, Luis CA, Kashuba A, Luis M, Harwood DG, Loewenstein D, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Dis Assoc Disord. 2002;16(4):203-12. Disponible en: https://doi.org/10.1097/00002093-200210000-00001

290. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology. 2013;80(19):1778-83. Disponible en: https://doi.org/10.1212/WNL.0b013e31828726f5

291. Aranda MP, Kremer IN, Hinton L, Zissimopoulos J, Whitmer RA, Hummel CH, et al. Impact of dementia: Health disparities, population trends, care interventions, and economic costs. J Am Geriatr Soc. 2021;69(7):1774-83. Disponible en: https://doi.org/10.1111/jgs.17345

292. Graham WV, Bonito-Oliva A, Sakmar TP. Update on Alzheimer's disease therapy and prevention strategies. Annu Rev Med. 2017;68(1):413-30. Disponible en: https://doi.org/10.1146/annurev-med-042915-103753

293. Eskandari S, Sajadimajd S, Alaei L, Soheilikhah Z, Derakhshankhah H, Bahrami G. Targeting common signaling pathways for the treatment of stroke and Alzheimer's: a comprehensive review. Neurotox Res. 2021;39(5):1589-612. Disponible en: https://doi.org/10.1007/s12640-021-00381-7

294. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors J, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals

from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-89. Disponible en: https://doi.org/10.1161/STR.0b013e318296aeca

295. Donnan GA, Baron JC, Ma H, Davis SM. Penumbral selection of patients for trials of acute stroke therapy. Lancet Neurol. 2009;8(3):261-9. Disponible en: https://doi.org/10.1016/S1474-4422(09)70041-9

296. Brainin M, Tuomilehto J, Heiss WD, Bornstein NM, Bath PMW, Teuschl Y, et al. Post-stroke cognitive decline: an update and perspectives for clinical research. Eur J Neurol. 2015;22(2):229-e16. Disponible en: https://doi.org/10.1111/ene.12626

297. Wang R, Qiu C, Dintica CS, Shang Y, Calderón Larrañaga A, Wang H, et al. Shared risk and protective factors between Alzheimer's disease and ischemic stroke: A population-based longitudinal study. Alzheimers Dement. 2021;17(2):191-204. Disponible en: https://doi.org/10.1002/alz.12203

298. Phipps MS, Cronin CA. Management of acute ischemic stroke. Bmj. 2020;368. Disponible en: https://doi.org/10.1136/bmj.l6983

299. Doria JW, Forgacs PB. Incidence, implications, and management of seizures following ischemic and hemorrhagic stroke. Curr Neurol Neurosci Rep. 2019;19(7):1-8. Disponible en: https://doi.org/10.1007/s11910-019-0957-4

300. Unnithan AKA, Das JM, Mehta P. Hemorrhagic Stroke. StatPearls Publishing; 2022; Disponible en: https://www.ncbi.nlm.nih.gov/books/NBK559173

301. Izzy S, Rubin DB, Ahmed FS, Akbik F, Renault S, Sylvester KW, et al. Cerebrovascular accidents during mechanical circulatory support. Stroke. mayo de 2018;49(5):1197-203. Disponible en: https://doi.org/10.1161/STROKEAHA.117.020002

302. Smith EE, Schneider JA, Wardlaw JM, Greenberg SM. Cerebral microinfarcts: the invisible lesions. Lancet Neurol. 2012;11(3):272-82. Disponible en: https://doi.org/10.1016/S1474-4422(11)70307-6

303. van Veluw SJ, Shih AY, Smith EE, Chen C, Schneider JA, Wardlaw JM, et al. Detection, risk factors, and functional consequences of cerebral microinfarcts. Lancet Neurol. 2017;16(9):730-40. Disponible en: https://doi.org/10.1016/S1474-4422(17)30196-5

304. Slooter AJ, Tang MX, van Duijn CM, Stern Y, Ott A, Bell K, et al. Apolipoprotein E ϵ4 and the risk of dementia with stroke: A population-based investigation. Jama. 1997;277(10):818-21. Disponible en: https://doi.org/10.1001/jama.1997.03540340052032

305. Belloy ME, Napolioni V, Greicius MD. A quarter century of APOE and Alzheimer's disease: progress to date and the path forward. Neuron. 2019;101(5):820-38. Disponible en: https://doi.org/10.1016/j.neuron.2019.01.056

306. Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pérez JM, Evans AC. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. Nat Commun. 2016;7(1):1-14. Disponible en: https://doi.org/10.1038/ncomms11934

307. de la Torre JC. Vascular risk factor detection and control may prevent Alzheimer's disease. Ageing Res Rev. 1 de julio de 2010;9(3):218-25. Disponible en: https://doi.org/10.1016/j.arr.2010.04.002

308. Lee PH, Bang OY, Hwang EM, Lee JS, Joo US, Mook-Jung I, et al. Circulating beta amyloid protein is elevated in patients with acute ischemic stroke. J Neural Transm. 1 de octubre de 2005;112(10):1371-9. Disponible en: https://doi.org/10.1007/s00702-004-0274-0

309. Smith EE. Cerebral amyloid angiopathy as a cause of neurodegeneration. J Neurochem. 2018;144(5):651-8. Disponible en: https://doi.org/10.1111/jnc.14157

310. Holland D, Desikan RS, Dale AM, McEvoy LK, Initiative for the ADN. Rates of decline in Alzheimer Disease decrease with age. PLOS ONE. 2 de agosto de 2012;7(8): e42325. Disponible en: https://doi.org/10.1371/journal.pone.0042325

311. Raji CA, Lopez OL, Kuller LH, Carmichael OT, Becker JT. Age, Alzheimer disease, and brain structure. Neurology. 1 de diciembre de 2009;73(22):1899-905. Disponible en: https://doi.org/10.1212/WNL.0b013e3181c3f293

312. Möller C, Vrenken H, Jiskoot L, Versteeg A, Barkhof F, Scheltens P, et al. Different patterns of gray matter atrophy in early- and late-onset Alzheimer's disease. Neurobiol Aging. 1 de agosto de 2013;34(8):2014-22. Disponible en: https://doi.org/10.1016/j.neurobiolaging.2013.02.013

313. Mendez MF. Early-onset Alzheimer disease and its variants. Contin Minneap Minn. 2019;25(1):34. Disponible en: https://doi.org/10.1212/CON.0000000000000687

314. Evans DA, Funkenstein HH, Albert MS, Scherr PA, Cook NR, Chown MJ, et al. Prevalence of Alzheimer's Disease in a community population of older persons: higher than previously reported. JAMA. 10 de noviembre de 1989;262(18):2551-6. Disponible en: https://doi.org/10.1001/jama.262.18.2551

315. Reitz C, Rogaeva E, Beecham GW. Late-onset vs nonmendelian early-onset Alzheimer disease: A distinction without a difference. Neurol Genet [Internet]. 1 de octubre de 2020 [citado 20 de febrero de 2022];6(5). Disponible en: Disponible en: https://doi.org/10.1212/NXG.0000000000000512

316. Nakayama H, Jørgensen HS, Raaschou HO, Olsen TS. The influence of age on stroke outcome. The Copenhagen Stroke Study. Stroke. abril de 1994;25(4):808-13. Disponible en: https://doi.org/10.1161/01.STR.25.4.808

317. Kelly-Hayes M. Influence of age and health behaviors on stroke risk: lessons from longitudinal studies. J Am Geriatr Soc. 2010;58(s2): S325-8. Disponible en: https://doi.org/10.1111/j.1532-5415.2010.02915.x

318. Barnes LL, Wilson RS, Bienias JL, Schneider JA, Evans DA, Bennett DA. Sex differences in the clinical manifestations of Alzheimer disease pathology. Arch Gen Psychiatry. 2005;62(6):685-91. Disponible en: https://doi.org/10.1001/archpsyc.62.6.685

319. Rabinowicz T, Dean DE, McDonald-Comber Petetot J, de Courten-Myers GM. Gender Differences in the human cerebral cortex: more neurons in males; more processes in females. J Child Neurol. 1 de febrero de 1999;14(2):98-107. Disponible en: https://doi.org/10.1177/088307389901400207

320. Ferretti MT, Iulita MF, Cavedo E, Chiesa PA, Schumacher Dimech A, Santuccione Chadha A, et al. Sex differences in Alzheimer disease - the gateway to precision medicine. Nat Rev Neurol. agosto de 2018;14(8):457-69. Disponible en: https://doi.org/10.1038/s41582-018-0032-9

321. Medrano Albero M, Boix Martínez R, Cerrato Crespán E, Ramírez Santa-Pau M. Incidencia y prevalencia de cardiopatía isquémica y enfermedad cerebrovascular en España: revisión sistemática de la literatura. Rev Esp Salud Pública. 2006;80(1):05-15. Disponible en: https://doi.org/10.1590/S1135-57272006000100002

322. Moriel M, Behar S, Tzivoni D, Hod H, Boyko V, Gottlieb S. Management and outcomes of elderly women and men with acute coronary syndromes in 2000 and 2002. Arch Intern Med. 2005;165(13):1521-6. Disponible en: https://doi.org/10.1001/archinte.165.13.1521

323. Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol. 1 de septiembre de 2008;7(9):812-26. Disponible en: https://doi.org/10.1016/S1474-4422(08)70169-8

324. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. The Lancet. 17 de diciembre de 2005;366(9503):2112-7. Disponible en: https://doi.org/10.1016/S0140-6736(05)67889-0

325. Singh G, Sharma M, Kumar GA, Rao NG, Prasad K, Mathur P, et al. The burden of neurological disorders across the states of India: the Global Burden of Disease Study 1990-2019. Lancet Glob Health. 1 de agosto de 2021;9(8): e1129-44. Disponible en: https://doi.org/10.1016/S2215-0366(19)30475-4

326. Parra MA, Baez S, Allegri R, Nitrini R, Lopera F, Slachevsky A, et al. Dementia in Latin America: assessing the present and envisioning the future. Neurology. 30 de enero de 2018;90(5):222-31. Disponible en: https://doi.org/10.1212/WNL.0000000000004897

327. Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016. N Engl J Med. 20 de diciembre de 2018;379(25):2429-37. Disponible en: https://doi.org/10.1056/NEJMoa1804492

328. Yatsuya H, Li Y, Hilawe EH, Ota A, Wang C, Chiang C, et al. Global trend in overweight and obesity and its association with cardiovascular disease incidence. Circ J. 2014; advpub: CJ-14-0850. Disponible en: https://doi.org/10.1253/circj.CJ-14-0850

329. Egger M, Smith GD, Sterne JA. Uses and abuses of meta-analysis. Clin Med. 2001;1(6):478. Disponible en: https://doi.org/10.7861/clinmedicine.1-6-478

330. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003;327(7414):557-60. Disponible en: https://doi.org/10.1136/bmj.327.7414.557

331. Pinho J, Quintas-Neves M, Dogan I, Reetz K, Reich A, Costa AS. Incident stroke in patients with Alzheimer's disease: systematic review and meta-analysis. Sci Rep. 2021;11(1):1-10. Disponible en: https://doi.org/10.1038/s41598-021-95821-x

332. Cao L, Tan L, Wang HF, Jiang T, Zhu XC, Yu JT. Cerebral microinfarcts and dementia: a systematic review and metaanalysis. Curr Alzheimer Res. 2017;14(7):802-8. Disponible en: https://doi.org/10.2174/1567205013666161201200429

333. Brayne C, Richardson K, Matthews FE, Fleming J, Hunter S, Xuereb JH, et al. Neuropathological correlates of dementia in over-80-year-old brain donors from the population-based cambridge city over-75s cohort (CC75C) study. J Alzheimers Dis. 1 de enero de 2009;18(3):645-58. Disponible en: https://doi.org/10.3233/JAD-2009-1182

334. Strozyk D, Dickson DW, Lipton RB, Katz M, Derby CA, Lee S, et al. Contribution of vascular pathology to the clinical expression of dementia. Neurobiol Aging. 1 de octubre de 2010;31(10):1710-20. Disponible en: https://doi.org/10.1016/j.neurobiolaging.2008.09.011

335. Troncoso JC, Zonderman AB, Resnick SM, Crain B, Pletnikova O, O'Brien RJ. Effect of infarcts on dementia in the Baltimore longitudinal study of aging. Ann Neurol. 2008;64(2):168-76. Disponible en: https://doi.org/10.1002/ana.21413

336. Bermejo-Pareja F, Benito-León J, Vega S, Medrano MJ, Román GC. Incidence and subtypes of dementia in three elderly populations of central Spain. J Neurol Sci. 15 de enero de 2008;264(1):63-72. Disponible en: https://doi.org/10.1016/j.jns.2007.07.021

337. Epstein NU, Xie H, Ruland SD, Pandey DK. Vascular risk factors and cardiovascular outcomes in the Alzheimer's Disease neuroimaging initiative. Am J Alzheimers Dis Dementias. 1 de junio de 2012;27(4):275-9. Disponible en: https://doi.org/10.1177/1533317512449730

338. Honig LS, Tang MX, Albert S, Costa R, Luchsinger J, Manly J, et al. Stroke and the risk of Alzheimer Disease. Arch Neurol. 1 de diciembre de 2003;60(12):1707-12. Disponible en: https://doi.org/10.1001/archneur.60.12.1707

339. Suter OC, Sunthorn T, Kraftsik R, Straubel J, Darekar P, Khalili K, et al. Cerebral hypoperfusion generates cortical watershed microinfarcts in Alzheimer Disease. Stroke. agosto de 2002;33(8):1986-92. Disponible en: https://doi.org/10.1161/01.STR.0000024523.82311.77

340. Arvanitakis Z, Leurgans SE, Barnes LL, Bennett DA, Schneider JA. Microinfarct pathology, dementia, and cognitive systems. Stroke. marzo de 2011;42(3):722-7. Disponible en: https://doi.org/10.1161/STROKEAHA.110.595082

341. Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G, Schellenberg GD, et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. Ann Neurol. 2007;62(4):406-13. Disponible en: https://doi.org/10.1002/ana.21208

342. Chen RL, Balami JS, Esiri MM, Chen LK, Buchan AM. Ischemic stroke in the elderly: an overview of evidence. Nat Rev Neurol. mayo de 2010;6(5):256-65. Disponible en: https://doi.org/10.1038/nrneurol.2010.36

343. Lucke-Wold BP, Turner RC, Logsdon AF, Simpkins JW, Alkon DL, Smith KE, et al. Common mechanisms of Alzheimer's Disease and ischemic stroke: the role of protein kinase c in the progression of age-related neurodegeneration. J Alzheimers Dis. 1 de enero de 2015;43(3):711-24. Disponible en: https://doi.org/10.3233/JAD-141422

344. Chi NF, Chien LN, Ku HL, Hu CJ, Chiou HY. Alzheimer disease and risk of stroke: A population-based cohort study. Neurology. 19 de febrero de 2013;80(8):705-11. Disponible en: https://doi.org/10.1212/WNL.0b013e31828250af

345. Vijayan M, Reddy PH. Stroke, Vascular Dementia, and Alzheimer's Disease: Molecular links. J Alzheimers Dis. 1 de enero de 2016;54(2):427-43. Disponible en: https://doi.org/10.3233/JAD-160527

346. Waziry R, Chibnik LB, Bos D, Ikram MK, Hofman A. Risk of hemorrhagic and ischemic stroke in patients with Alzheimer disease: A synthesis of the literature. Neurology. 11 de febrero de 2020;94(6):265-72. Disponible en: https://doi.org/10.1212/WNL.0000000000008924

347. Tolppanen AM, Lavikainen P, Solomon A, Kivipelto M, Soininen H, Hartikainen S. Incidence of stroke in people with Alzheimer disease: A national register-based approach. Neurology. 22 de enero de 2013;80(4):353-8. Disponible en: https://doi.org/10.1212/WNL.0b013e31827f08c5

348. Jellinger KA. Alzheimer disease and cerebrovascular pathology: an update. J Neural Transm. 2002;109(5):813-36. Disponible en: https://doi.org/10.1007/s007020200068

349. Lin X, Fan Y, Zhang F, Lin Y. Cerebral microinfarct is emergency consequence of Alzheimer's disease: a new insight into development of neurodegenerative diseases. Int J Biol Sci. 24 de enero de 2022;18(4):1569-79. Disponible en: https://doi.org/10.7150/ijbs.55419

350. Saposnik G, Black SE, Hakim A, Fang J, Tu JV, Kapral MK. Age Disparities in Stroke Quality of Care and Delivery of Health Services. Stroke. octubre de 2009;40(10):3328-35. Disponible en: https://doi.org/10.1161/STROKEAHA.109.558759

351. Ferro D, Heinen R, de Brito Robalo B, Kuijf H, Biessels GJ, Reijmer Y. Cortical microinfarcts and white matter connectivity in memory clinic patients. Front Neurol [Internet]. 2019 [citado 24 de noviembre de 2022];10. Disponible en: https://doi.org/10.3389/fneur.2019.00571

352. Kawas C, Gray S, Brookmeyer R, Fozard J, Zonderman A. Age-specific incidence rates of Alzheimer's disease: The Baltimore Longitudinal Study of Aging. Neurology. 13 de junio de 2000;54(11):2072-7. Disponible en: https://doi.org/10.1212/WNL.54.11.2072

353. Roy-O'Reilly M, McCullough LD. Age and sex are critical factors in ischemic stroke pathology. endocrinology. 1 de agosto de 2018;159(8):3120-31. Disponible en: https://doi.org/10.1210/en.2018-00465

354. Haast RA, Gustafson DR, Kiliaan AJ. Sex differences in stroke. J Cereb Blood Flow Metab. 1 de diciembre de 2012;32(12):2100-7. Disponible en: https://doi.org/10.1038/jcbfm.2012.141

355. Cook M, Baker N, Lanes S, Bullock R, Wentworth C, Arrighi HM. Incidence of stroke and seizure in Alzheimer's disease dementia. Age Ageing. 1 de julio de 2015;44(4):695-9. Disponible en: https://doi.org/10.1093/ageing/afv061

356. Michalski D, Keck AL, Grosche J, Martens H, Härtig W. Immunosignals of oligodendrocyte markers and myelin-associated proteins are critically affected after experimental stroke in wild-type and alzheimer modeling mice of different ages. Front Cell Neurosci [Internet]. 2018 [citado 23 de enero de 2023];12. Disponible en: https://doi.org/10.3389/fncel.2018.00023

357. Kokmen E, Whisnant JP, O'Fallon WM, Chu CP, Beard CM. Dementia after ischemic stroke: A population-based study in Rochester, Minnesota (1960-1984). Neurology. 1 de enero de 1996;46(1):154-9. Disponible en: https://doi.org/10.1212/WNL.46.1.154

358. Ivan CS, Seshadri S, Beiser A, Au R, Kase CS, Kelly-Hayes M, et al. Dementia after stroke. Stroke. junio de 2004;35(6):1264-8. Disponible en: https://doi.org/10.1161/01.STR.0000127810.92616.78

359. Wolters FJ, Chibnik LB, Waziry R, Anderson R, Berr C, Beiser A, et al. Twenty-seven-year time trends in dementia incidence in Europe and the United States: The Alzheimer Cohorts Consortium. Neurology. 4 de agosto de 2020;95(5): e519-31. Disponible en: https://doi.org/10.1212/WNL.0000000000010022

360. Soto JA, Guillén Grima F, Morales G, Muñoz S, Aguinaga Ontoso I, Fuentes Aspe R. Prevalencia e incidencia de ictus en Europa: revisión sistemática y metaanálisis. An Sist Sanit Navar. 2022;45(1):12-12. Disponible en: https://doi.org/10.23938/ASSN.0979

361. Paterson KE, Myint PK, Jennings A, Bain LKM, Lentjes MAH, Khaw KT, et al. Mediterranean diet reduces risk of incident stroke in a population with varying cardiovascular disease risk profiles. Stroke. octubre de 2018;49(10):2415-20. Disponible en: https://doi.org/10.1161/STROKEAHA.117.020258

362. Román GC, Jackson RE, Reis J, Román AN, Toledo JB, Toledo E. Extra-virgin olive oil for potential prevention of Alzheimer disease. Rev Neurol (Paris). 1 de diciembre de 2019;175(10):705-23. Disponible en: https://doi.org/10.1016/j.neurol.2019.07.017

363. Zurique Sánchez C, Cadena Sanabria MO, Zurique Sánchez M, Camacho López PA, Sánchez Sanabria M, Hernández Hernández S, et al. Prevalencia de demencia en adultos mayores de América Latina: revisión sistemática. Rev Esp Geriatría Gerontol. 1 de noviembre de 2019;54(6):346-55. Disponible en: https://doi.org/10.1016/j.regg.2018.12.007

364. Jorgensen N, Cabañas M, Oliva J, Rejas J, León T. Los costes de los cuidados informales asociados a enfermedades neurológicas discapacitantes de alta prevalencia en España. Neurol Barc Ed Impr. 2008;23(1):29-39. Disponible en: https://pesquisa.bvsalud.org/portal/resource/pt/ibc-63206

365. Mayeux R, Stern Y. Epidemiology of Alzheimer Disease. Cold Spring Harb Perspect Med. 8 de enero de 2012;2(8): a006239. Disponible en: https://doi.org/10.1101/cshperspect.a006239

366. Silva MVF, Loures C de MG, Alves LCV, de Souza LC, Borges KBG, Carvalho M das G. Alzheimer's disease: risk factors and potentially protective measures. J Biomed Sci. 9 de mayo de 2019;26(1):33. Disponible en: https://doi.org/10.1186/s12929-019-0524-y

367. Regalado Doña PJ, Azpiazu Artigas P, Sánchez Guerra ML, Almenar Monfort C. Factores de riesgo vascular y enfermedad de Alzheimer. Rev Esp Geriatría Gerontol. 1 de marzo de 2009;44(2):98-105. Disponible en: https://doi.org/10.1016/j.regg.2008.12.004

368. Kalaria RN. The role of cerebral ischemia in Alzheimer's disease. Neurobiol Aging. 1 de marzo de 2000;21(2):321-30. Disponible en: https://doi.org/10.1016/S0197-4580(00)00125-1

369. Luchsinger JA, Tang MX, Shea S, Mayeux R. Hyperinsulinemia and risk of Alzheimer disease. Neurology. 12 de octubre de 2004;63(7):1187-92. Disponible en: https://doi.org/10.1212/01.WNL.0000140292.04932.87

370. Lipton RB, Schwedt TJ, Friedman BW. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1545-602. Disponible en: https://doi.org/10.1016/S0140-6736(16)31678-6

371. Hua Y, Wang B, Wallen GR, Shao P, Ni C, Hua Q. Health-Promoting Lifestyles and Depression in Urban Elderly Chinese. PLOS ONE. 17 de marzo de 2015;10(3): e0117998. Disponible en: https://doi.org/10.1371/journal.pone.0117998

372. Xue Y, Lu J, Zheng X, Zhang J, Lin H, Qin Z, et al. The relationship between socioeconomic status and depression among the older adults: The mediating role of health promoting lifestyle. J Affect Disord. 15 de abril de 2021; 285:22-8. Disponible en: https://doi.org/10.1016/j.jad.2021.01.085

373. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer Disease: Systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry. 1 de mayo de 2006;63(5):530-8. Disponible en: Disponible en: https://doi.org/10.1001/archpsyc.63.5.530

374. Feringa FM, van der Kant R. Cholesterol and Alzheimer's Disease; From Risk Genes to Pathological Effects. Front Aging Neurosci [Internet]. 2021 [citado 16 de febrero de 2023];13. Disponible en: https://doi.org/10.3389/fnagi.2021.690372

375. Laufs U, Parhofer KG, Ginsberg HN, Hegele RA. Clinical review on triglycerides. Eur Heart J. 1 de enero de 2020;41(1):99-109c. Disponible en: https://doi.org/10.1093/eurheartj/ehz785

376. Duron E, Hanon O. Vascular risk factors, cognitve decline, and dementia. Vasc Health Risk Manag. 31 de diciembre de 2008;4(2):363-81. Disponible en: https://doi.org/10.2147/VHRM.S1839

377. Knecht S, Oelschläger C, Duning T, Lohmann H, Albers J, Stehling C, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. Eur Heart J. 1 de septiembre de 2008;29(17):2125-32. Disponible en: https://doi.org/10.1093/eurheartj/ehn341

378. Imtiaz B, Tolppanen AM, Kivipelto M, Soininen H. Future directions in Alzheimer's disease from risk factors to prevention. Biochem Pharmacol. 2014;88(4):661-70. Disponible en: https://doi.org/10.1016/j.bcp.2014.01.003

379. Guerreiro R, Bras J. The age factor in Alzheimer's disease. Genome Med. 20 de octubre de 2015;7(1):106. Disponible en: https://doi.org/10.1186/s13073-015-0232-5

380. Cehajic Kapetanovic J, Patrício MI, MacLaren RE. Progress in the development of novel therapies for choroideremia. Expert Rev Ophthalmol. 2 de noviembre de 2019;14(6):277-85. Disponible en: https://doi.org/10.1080/17469899.2019.1699406

381. Kaur S, Baine MJ, Jain M, Sasson AR, Batra SK. Early diagnosis of pancreatic cancer: challenges and new developments. Biomark Med. octubre de 2012;6(5):597-612. Disponible en: https://doi.org/10.2217/bmm.12.69

382. Richard MA, Grob JJ, Avril MF, Delaunay M, Thirion X, Wolkenstein P, et al. Melanoma and tumor thickness: challenges of early diagnosis. Arch Dermatol. 1 de marzo de 1999;135(3):269-74. Disponible en: https://doi.org/10.1001/archderm.135.3.269

383. Tschoepe D, Roesen P. Heart disease in diabetes mellitus: A challenge for early diagnosis and intervention. Exp Clin Endocrinol Diabetes. 1998;106(1):16-24. Disponible en: https://doi.org/10.1055/s-0029-1211944

384. Nordberg A. Towards early diagnosis in Alzheimer disease. Nat Rev Neurol. febrero de 2015;11(2):69-70. Disponible en: https://doi.org/10.1038/nrneurol.2014.257

385. Hall MA. Correlation-based feature selection for machine learning [Internet] [Thesis]. The University of Waikato; 1999 [citado 18 de noviembre de 2022]. Disponible en: https://researchcommons.waikato.ac.nz/handle/10289/15043

386. Kononenko I. Estimating attributes: Analysis and extensions of RELIEF. En: Bergadano F, De Raedt L, editores. Machine Learning: ECML-94. Berlin, Heidelberg: Springer; 1994. p. 171-82. (Lecture Notes in Computer Science). Disponible en: https://doi.org/10.1007/3-540-57868-4_57

387. Amézquita Moreno GI, Patiño Cañas N, Morales Salamanca CC. Minería de datos para la identificación de factores de riesgo en pacientes con hipertensión arterial. Fundación Universtitaria Unipanamericana Compensar. 2019. Disponible en: https://repositoriocrai.ucompensar.edu.co/handle/compensar/2293

388. Alonso SG, de la Torre-Díez I, Hamrioui S, López-Coronado M, Barreno DC, Nozaleda LM, et al. Data Mining Algorithms and Techniques in Mental Health: A Systematic Review. J Med Syst. 21 de julio de 2018;42(9):161. https://doi.org/10.1007/s10916-018-1018-2

389. Shipe ME, Deppen SA, Farjah F, Grogan EL. Developing prediction models for clinical use using logistic regression: an overview. J Thorac Dis. marzo de 2019;11(Suppl 4): S574-84. Disponible en: https://doi.org/10.21037/jtd.2019.01.25

390. Adams KM. Linear discriminant analysis in clinical neuropsychology research. J Clin Neuropsychol. 1 de noviembre de 1979;1(3):259-72. Disponible en: https://doi.org/10.1080/01688637908414455

391. Pisner DA, Schnyer DM. Chapter 6 - Support vector machine. En: Mechelli A, Vieira S, editores. Machine Learning [Internet]. Academic Press; 2020 [citado 24 de noviembre de 2022]. p. 101-21. Disponible en: https://doi.org/10.1016/B978-0-12-815739-8.00006-7

392. Penny W, Frost D. Neural Networks in Clinical Medicine. Med Decis Making. 1 de octubre de 1996;16(4):386-98. Disponible en: https://doi.org/10.1177/0272989X9601600409

393. Podgorelec V, Kokol P, Stiglic B, Rozman I. Decision Trees: An Overview and Their Use in Medicine. J Med Syst. 1 de octubre de 2002;26(5):445-63. Disponible en: https://doi.org/10.1023/A:1016409317640

394. Khamis HS, Cheruiyot KW, Kimani S. Application of k-nearest neighbour classification in medical data mining. Int J Inf Commun Technol Res. 2014;4(4). Disponible en: https://www.researchgate.net/profile/Hassan-Shee/publication/270163293_Application_of_k-

Nearest_Neighbour_Classification_in_Medical_Data_Mining/links/54a249fd0cf256bf8baf7fff/Application-of-k-Nearest-Neighbour-Classification-in-Medical-Data-Mining.pdf

395. Soni J, Ansari U, Sharma D, Soni S. Predictive data mining for medical diagnosis: An overview of heart disease prediction. Int J Comput Appl. 2011;17(8):43-8. Disponible en: https://doi.org/10.5120/2237-2860

396. Chu LW. Alzheimer's disease: early diagnosis and treatment. Hong Kong Med J. 2012;18(3):228-37. Disponible en: https://www.hkmj.org/system/files/hkm1206p228.pdf

397. Wolberg WH, Street WN, Mangasarian OL. Machine learning techniques to diagnose breast cancer from image-processed nuclear features of fine needle aspirates. Cancer Lett. 15 de marzo de 1994;77(2):163-71. Disponible en: https://doi.org/10.1016/0304-3835(94)90099-X

398. Abdel-Basset M, Ding W, El-Shahat D. A hybrid Harris Hawks optimization algorithm with simulated annealing for feature selection. Artif Intell Rev. 1 de enero de 2021;54(1):593-637. Disponible en: https://doi.org/10.1007/s10462-020-09860-3

399. Xue B, Zhang M, Browne WN, Yao X. A Survey on evolutionary computation approaches to feature selection. IEEE Trans Evol Comput. agosto de 2016;20(4):606-26. Disponible en: https://doi.org/10.1109/TEVC.2015.2504420

400. Li J, Cheng K, Wang S, Morstatter F, Trevino RP, Tang J, et al. Feature selection: a data perspective. ACM Comput Surv. 6 de diciembre de 2017;50(6): 94:1-94:45. Disponible en: https://doi.org/10.1145/3136625

401. Das S, Singh PK, Bhowmik S, Sarkar R, Nasipuri M. A harmony search based wrapper feature selection method for holistic bangla word recognition. Procedia Comput Sci. 1 de enero de 2016; 89:395-403. Disponible en: https://doi.org/10.1016/j.procs.2016.06.087

402. Estevez PA, Tesmer M, Perez CA, Zurada JM. Normalized mutual information feature selection. IEEE Trans Neural Netw. febrero de 2009;20(2):189-201. Disponible en: https://doi.org/10.1109/TNN.2008.2005601

403. Dwivedi R, Kumar R, Jangam E, Kumar V. An ant colony optimization based feature selection for data classification. Int J Recent Technol Eng. 2019; 7:35-40. Disponible en: https://www.researchgate.net/profile/Rajesh-Dwivedi-4/publication/358351487_E10070275S419/links/61fd2ea84393577abe0ef31b/E10070275S419.pdf

404. Liu M, Zhang D. Feature selection with effective distance. Neurocomputing. 26 de noviembre de 2016; 215:100-9. Disponible en: https://doi.org/10.1016/j.neucom.2015.07.155

405. Chantar H, Thaher T, Turabieh H, Mafarja M, Sheta A. BHHO-TVS: A binary harris hawks optimizer with time-varying scheme for solving data classification problems. Appl Sci. enero de 2021;11(14):6516. Disponible en: https://doi.org/10.3390/app11146516

406. Su CT, Hsu JH. An extended Chi2 algorithm for discretization of real value attributes. IEEE Trans Knowl Data Eng. marzo de 2005;17(3):437-41. Disponible en: https://doi.org/10.1109/TKDE.2005.39

407. Gu Q, Li Z, Han J. Generalized Fisher Score for Feature Selection [Internet]. arXiv; 2012 [citado 18 de noviembre de 2022]. Disponible en: Disponible en: http://arxiv.org/abs/1202.3725

408. Yu L, Liu H. Feature selection for high-dimensional data: A fast correlation-based filter solution. En: Proceedings of the 20th international conference on machine learning (ICML-03). 2003. p. 856-63.

409. Xue B, Zhang M, Browne WN. Particle swarm optimisation for feature selection in classification: Novel initialisation and updating mechanisms. Appl Soft Comput. 1 de mayo de 2014; 18:261-76. Disponible en: https://doi.org/10.1016/j.asoc.2013.09.018

410. Too J, Abdullah AR. Opposition based competitive grey wolf optimizer for EMG feature selection. Evol Intell. 1 de diciembre de 2021;14(4):1691-705. Disponible en: https://doi.org/10.1007/s12065-020-00441-5

411. Sainin MS, Alfred R. A genetic based wrapper feature selection approach using Nearest Neighbour Distance Matrix. En: 2011 3rd Conference on Data Mining and Optimization (DMO). 2011. p. 237-42. Disponible en: https://doi.org/10.1109/DMO.2011.5976534

412. Emary E, Zawbaa HM, Hassanien AE. Binary grey wolf optimization approaches for feature selection. Neurocomputing. 8 de enero de 2016; 172:371-81. Disponible en: https://doi.org/10.1016/j.neucom.2015.06.083

413. Rodrigues D, Yang XS, de Souza AN, Papa JP. Binary flower pollination algorithm and its application to feature selection. En: Yang XS, editor. Recent advances in swarm intelligence and evolutionary computation [Internet]. Cham: Springer International Publishing; 2015 [citado 25 de noviembre de 2022]. p. 85-100. (Studies in Computational Intelligence). Disponible en: https://doi.org/10.1007/978-3-319-13826-8_5 https://doi.org/10.1007/978-3-319-13826-8_5

414. AbdEl-Fattah Sayed S, Nabil E, Badr A. A binary clonal flower pollination algorithm for feature selection. Pattern Recognit Lett. 1 de julio de 2016; 77:21-7. Disponible en: https://doi.org/10.1016/j.patrec.2016.03.014

415. Rodrigues D, Pereira LAM, Nakamura RYM, Costa KAP, Yang XS, Souza AN, et al. A wrapper approach for feature selection based on Bat Algorithm and Optimum-Path Forest. Expert Syst Appl. 1 de abril de 2014;41(5):2250-8. Disponible en: https://doi.org/10.1016/j.eswa.2013.09.023

416. Nakamura RYM, Pereira LAM, Costa KA, Rodrigues D, Papa JP, Yang XS. BBA: A Binary Bat Algorithm for Feature Selection. En: 2012 25th SIBGRAPI Conference on Graphics, Patterns and Images. 2012. p. 291-7. Disponible en: https://doi.org/10.1109/SIBGRAPI.2012.47

417. Jameel S, Rehman SU. An optimal feature selection method using a modified wrapper-based ant colony optimisation. J Natl Sci Found Sri Lanka. 2018;46(2):143-51. Disponible en: https://doi.org/10.4038/jnsfsr.v46i2.8414

418. Too J, Mafarja M, Mirjalili S. Spatial bound whale optimization algorithm: an efficient high-dimensional feature selection approach. Neural Comput Appl. 1 de diciembre de 2021;33(23):16229-50. Disponible en: https://doi.org/10.1007/s00521-021-06224-y

419. Mafarja M, Mirjalili S. Whale optimization approaches for wrapper feature selection. Appl Soft Comput. 1 de enero de 2018; 62:441-53. Disponible en: https://doi.org/10.1016/j.asoc.2017.11.006

420. Too J, Abdullah AR, Mohd Saad N. A New Co-Evolution Binary Particle Swarm Optimization with Multiple Inertia Weight Strategy for Feature Selection. Informatics. junio de 2019;6(2):21. Disponible en: https://doi.org/10.3390/informatics6020021

421. Zheng L, Diao R, Shen Q. Efficient feature selection using a self-adjusting harmony search algorithm. En: 2013 13th UK Workshop on Computational Intelligence (UKCI). 2013. p. 167-74. Disponible en: https://doi.org/10.1109/UKCI.2013.6651302

422. Pacheco J, Casado S, Núñez L. A variable selection method based on Tabu search for logistic regression models. Eur J Oper Res. 1 de diciembre de 2009;199(2):506-11. Disponible en: https://doi.org/10.1016/j.ejor.2008.10.007

423. Tahir MA, Smith J. Feature selection using intensified tabu search for supervised classification. 2008;

424. Queen O, Emrich SJ. LASSO-based feature selection for improved microbial and microbiome classification. En: 2021 IEEE International Conference on Bioinformatics and Biomedicine (BIBM). 2021. p. 2301-8. Disponible en: https://doi.org/10.1109/BIBM52615.2021.9669485

425. Liu H, Zhou M, Liu Q. An embedded feature selection method for imbalanced data classification. IEEECAA J Autom Sin. mayo de 2019;6(3):703-15. Disponible en: https://doi.org/10.1109/JAS.2019.1911447

426. Pacheco J, Casado S, Nuñez L. Use of VNS and TS in classification: variable selection and determination of the linear discrimination function coefficients. IMA J Manag Math. 1 de abril de 2007;18(2):191-206. Disponible en: https://doi.org/10.1093/imaman/dpm012

427. Remeseiro B, Bolon-Canedo V. A review of feature selection methods in medical applications. Comput Biol Med. 1 de septiembre de 2019; 112:103375. Disponible en: https://doi.org/10.1016/j.compbiomed.2019.103375

428. Inbarani HH. Hybrid Tolerance Rough Set-Firefly based supervised feature selection for MRI brain tumor image classification. Appl Soft Comput. 1 de septiembre de 2016; 46:639-51. Disponible en: https://doi.org/10.1016/j.asoc.2016.03.014

429. Dimitriadis SI, Liparas D, Tsolaki MN. Random forest feature selection, fusion and ensemble strategy: Combining multiple morphological MRI measures to discriminate among healhy elderly, MCI, cMCI and alzheimer's disease patients: From the alzheimer's disease neuroimaging initiative (ADNI) database. J Neurosci Methods. 15 de mayo de 2018; 302:14-23. Disponible en: https://doi.org/10.1016/j.jneumeth.2017.12.010

430. Liu X, Ma L, Song L, Zhao Y, Zhao X, Zhou C. Recognizing common CT imaging signs of lung diseases through a new feature selection method based on fisher criterion and genetic optimization. IEEE J Biomed Health Inform. marzo de 2015;19(2):635-47. Disponible en: https://doi.org/10.1109/JBHI.2014.2327811

431. Chong DY, Kim HJ, Lo P, Young S, McNitt-Gray MF, Abtin F, et al. Robustness-driven feature selection in classification of fibrotic interstitial lung disease patterns in computed tomography using 3D texture features. IEEE Trans Med Imaging. enero de 2016;35(1):144-57. Disponible en: https://doi.org/10.1109/TMI.2015.2459064

432. Shi Y, Gao Y, Liao S, Zhang D, Gao Y, Shen D. A learning-based CT prostate segmentation method via joint transductive feature selection and regression. Neurocomputing. 15 de enero de 2016; 173:317-31. Disponible en: https://doi.org/10.1016/j.neucom.2014.11.098

433. Guinin M, Ruan S, Dubray B, Massoptier L, Gardin I. Notice of Removal: Feature selection and patch-based segmentation in MRI for prostate radiotherapy. En: 2016 IEEE International Conference on Image Processing (ICIP). 2016. p. 2663-7. Disponible en: https://doi.org/10.1109/ICIP.2016.7532842

434. Sahran S, Albashish D, Abdullah A, Shukor NA, Hayati Md Pauzi S. Absolute cosine-based SVM-RFE feature selection method for prostate histopathological grading. Artif Intell Med. 1 de mayo de 2018; 87:78-90. Disponible en: https://doi.org/10.1016/j.artmed.2018.04.002

435. Jain I, Jain VK, Jain R. Correlation feature selection based improved-Binary Particle Swarm Optimization for gene selection and cancer classification. Appl Soft Comput. 1 de enero de 2018; 62:203-15. Disponible en: https://doi.org/10.1016/j.asoc.2017.09.038

436. Wang H, Jing X, Niu B. A discrete bacterial algorithm for feature selection in classification of microarray gene expression cancer data. Knowl-Based Syst. 15 de junio de 2017; 126:8-19. Disponible en: https://doi.org/10.1016/j.knosys.2017.04.004

437. Kang C, Huo Y, Xin L, Tian B, Yu B. Feature selection and tumor classification for microarray data using relaxed Lasso and generalized multi-class support vector machine. J Theor Biol. 21 de febrero de 2019; 463:77-91. Disponible en: https://doi.org/10.1016/j.jtbi.2018.12.010

438. Niwas SI, Lin W, Bai X, Kwoh CK, Sng CC, Aquino MC, et al. Reliable Feature Selection for Automated Angle Closure Glaucoma Mechanism Detection. J Med Syst. 8 de febrero de 2015;39(3):21. Disponible en: https://doi.org/10.1007/s10916-015-0199-1

439. Pacheco J, Caballero R, Laguna M, Molina J. Bi-objective bus routing: an aplicación to school buses in rural areas. Transportation Science. 2013; 47 (3): 397-411. Disponible en: https://doi.org/10.1287/trsc.1120.0437

440. Rais ATQKS. HM Mirjalili S Alhussian H. Bin optim using hybrid grey wolf optim feature sel IEEE Access. 2019; 7:39496-508. Disponible en: https://doi.org/10.1109/ACCESS.2019.2906757

441. Mirjalili S, Lewis A. The Whale Optimization Algorithm. Adv Eng Softw. 1 de mayo de 2016; 95:51-67. Disponible en: https://doi.org/10.1016/j.advengsoft.2016.01.008

442. Yang XS. Flower Pollination Algorithm for Global Optimization. En: Durand-Lose J, Jonoska N, editores. Unconventional Computation and Natural Computation. Berlin, Heidelberg: Springer; 2012. p. 240-9. (Lecture Notes in Computer Science). Disponible en: https://doi.org/10.1007/978-3-642-32894-7_27

443. Meilán JJG, Gutiérrez JMC. Enfermedad de Alzheimer y otras demencias neurodegenerativas: Aspectos psicosociales. Elsevier España; 2017.

444. Abizanda P, Jordán J. Conocer para aceptar. Enfermedad de Alzheimer. Cuenca: Ediciones de la Universidad de Castilla-La Mancha; 2011.

445. INE. Instituto nacional de estadística; avance del Padrón nacional a 1 de enero de 2018 (datos provisionales). Nota de prensa, INE, 28 de julio de 2018. [Internet]. Disponible en: http://www.ine.es/prensa/cp_e2018_p.pdf

446. Organización mundial de la salud. Envejecimiento y ciclo de vida. 10 datos sobre el envejecimiento y ciclo de vida [Internet]. [Internet]. Madrid: Organización Mundial de la Salud; 2018 07-28. Disponible en: http://www.who.int/es/news-room/fact-sheets/detail/envejecimiento-y-salud

447. INE. Defunciones según la causa de muerte. Notas de prensa. [Internet]. 2016. Disponible en: www.ine.es/prensa/prensa.htm

448. Nolasc Acarín AM. Alzheimer: envejecimiento y demencia. 1a edición. Barcelona: RBA; 2017.

449. Gobierno de España. Ministerio de Sanidad servicios sociales e igualdad. I. INFORME 2016. Las personas mayores en España. Datos estadísticos estatales y por comunidades autónomas. [Internet]. Madrid; 2017. Disponible en: www.imserso.es

450. Gobierno de M de S Consumo y Bienestar Social. Encuesta europea de salud para España [Internet]. 2014 01. Disponible en: http://www.mscbs.gob.es/estadEstudios/estadisticas/EncuestaEuropea/pdf/EESE14_inf.pdf

451. Fombuena NG. La psicometría de las demencias a debate. Neurología. 2007;22(5):301-11. Disponible en: http://public-files.prbb.org/publicacions/10950703010311.pdf

452. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001;56(9):1133-42. Disponible en: https://doi.org/10.1212/WNL.56.9.1133

453. Robles A, Del Ser T, Alom J, Pena-Casanova J. Propuesta de criterios para el diagnóstico clínico del deterioro cognitivo ligero, la demencia y la enfermedad de Alzheimer. Neurología. 2002;17(1):17-32. Disponible en: https://medes.com/publication/3693

454. Salud (Ginebra) OM de la. Cie 10. Trastornos mentales y del comportamiento: descripciones clínicas y pautas para el diagnóstico. Meditor; 1992.

455. Martín-Vegue AR, Vázquez-Barquero JL, Castanedo SH. CIE-10 (I): Introducción, historia y estructura general. Papeles Méd. 2002;11(1):24-35. Disponible en: https://web.archive.org/web/20180428021850id_/http://sedom.es/wp-content/themes/sedom/pdf/4cbc708c6225apm-11-1-005.pdf

456. López-Álvarez J, Agüera-Ortiz LF. Nuevos criterios diagnósticos de la demencia y la enfermedad de Alzheimer: una visión desde la psicogeriatría. Psicogeriatria. 2015;5(1):3-14. Disponible en: https://www.viguera.com/sepg/pdf/revista/0501/501_0003_0014.pdf

457. Lopez CA. Manual diagnóstico y estadístico de los trastornos mentales: DSM-5. Editorial medica panamericana; 2014.

458. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 05 de 2011;7(3):263-9. Disponible en: https://doi.org/10.1016/j.jalz.2011.03.005

459. Romero JS, González MG, Marante JPD, Llibre Guerra JJ. Factores de riesgo de la enfermedad de Alzheimer. Rev Hosp Psiquiátrico Habana. 2014;11(3). Disponible en: https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=55585

460. Barranco-Quintana JL, Allam MF, Del Castillo AS, Navajas RFC. Factores de riesgo de la enfermedad de Alzheimer. Rev Neurol. 2005;40(10):613-8. Disponible en: https://doi.org/10.33588/rn.4010.2004360

461. Joan Deus Yela, Josep Deví Bastida, Pilar D. Neuropsicología de la enfermedad de Alzheimer. Madrid: Síntesis, D. L; 2018.

462. Fuentes P. Enfermedad de Alzheimer: una nota histórica. Rev Chil Neuro-Psiquiatr. 2003; 41:9-12. Disponible en: https://doi.org/10.4067/S0717-92272003041200002

463. García Rodríguez F, Ceballos Atienza R. Enfermedad de Alzheimer y calidad de vida. Editor Alcalá SL Madr. 2002.

464. Rodríguez D, Formiga F, Fort I, Robles MJ, Barranco E, Cubí D. Tratamiento farmacológico de la demencia: cuándo, cómo y hasta cuándo. Recomendaciones del Grupo de Trabajo de Demencias de la Sociedad Catalana de Geriatría y Gerontología. Rev Esp Geriatría Gerontol. 2012;47(5):228-33. Disponible en: https://doi.org/10.1016/j.regg.2012.02.008

465. Fuentes P, Slachevsky Ch A. Enfermedad de Alzheimer: Actualización en terapia farmacológica. Rev Médica Chile. 2005;133(2):224-30. Disponible en: https://doi.org/10.4067/S0034-98872005000200012

466. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol. 2014;13(8):788-94. Disponible en: https://doi.org/10.1016/S1474-4422(14)70136-X

467. Tangney CC, Li H, Wang Y, Barnes L, Schneider JA, Bennett DA, et al. Relation of DASH-and Mediterranean-like dietary patterns to cognitive decline in older persons. Neurology. 2014;83(16):1410-6. Disponible en: https://doi.org/10.1212/WNL.0000000000000884

468. Caballero AIB. History of the statistics teaching in Spain: a short study. BEIO Bol Estad E Investig Oper. 2014;30(2):161-80. Disponible en: https://dialnet.unirioja.es/servlet/articulo?codigo=5021296

469. Obispo Monge J. Relación entre los niveles de glucemia y hemoglobina glicosilada en la diabetes mellitus tipo II. Relación entre los niveles glucemia hemoglobina glicosilada en Diabetes mellitus tipo II. 1992;53-53. Disponible en: https://pesquisa.bvsalud.org/portal/resource/pt/lil-187008

470. Flack JM, Adekola B. Blood pressure and the new ACC/AHA hypertension guidelines. Trends Cardiovasc Med. 2020;30(3):160-4. Disponible en: https://doi.org/10.1016/j.tcm.2019.05.003

471. Saladrigas MV. El sistema de clasificación ATC de sustancias farmacéuticas para uso humano. Panace. 2004; 5 (15): 59-67. Disponible en: https://www.tremedica.org/wp-content/uploads/n15_tribuna-Saladrigas.pdf

472. Persson KB, Strøm H. The Anatomical Therapeutic Chemical (ATC) Classification and Its Use In The Nordic Countries. En: Meeting of Head of WHO Collaborating Centres for

The Classification of Dissease, Brisbane, Queensland, Australia Departemen Anak Rumkital Dr Ramelan Surabaya), Majalah Ilmu Kefarmasian. 2002. p. 3.

473. del Estado BO. Real decreto 1348/2003, de 31 de octubre, por el que se adapta la clasificación anatómica de medicamentos al sistema de clasificación ATC. Bol Of Estado No2644-11-2003 Rect Bol Of Estado No2124-1-2004. 2003;

474. Castro LR. Consideraciones éticas en el desarrollo de investigaciones de Terapia Ocupacional. Rev Chil Ter Ocupacional. 2021;22(2):253-8. Disponible en: https://doi.org/10.5354/0719-5346.2004.158

475. Avanzas P, Bayes-Genis A, P&#x000E9, rez de Isla L, Sanchis J, Heras M. Consideraciones éticas de la publicación de artículos científicos. Rev Esp Cardiol. 1 de mayo de 2011;64(05):427-9. Disponible en: https://doi.org/10.1016/j.recesp.2011.02.006

476. Sinai J. National Research Council of the National Academies. Intelligence Analysis: Behavioral and Social Scientific Foundations. JSTOR; 2013.

477. Rodríguez Yunta E. Comités de evaluación ética y científica para la investigación en seres humanos y las pautas CIOMS 2002. Acta Bioethica. 2004;10(1):37-48. Disponible en: https://doi.org/10.4067/S1726-569X2004000100005

478. Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales [Internet]. Noticias Jurídicas. [citado 5 de marzo de 2019]. Disponible en: http://noticias.juridicas.com/base_datos/Laboral/632849-lo-3-2018-de-5-dic-proteccion-de-datos-personales-y-garantia-de-los-derechos.html

479. WMA - The World Medical Association-Declaración de Helsinki de la AMM - Principios éticos para las investigaciones médicas en seres humanos [Internet]. [citado 5 de marzo de 2019]. Disponible en: https://www.wma.net/es/policies-post/declaracion-de-helsinki-de-la-amm-principios-eticos-para-las-investigaciones-medicas-en-seres-humanos/

480. Comisión de Bioética | Universidad de Burgos [Internet]. [citado 5 de marzo de 2019]. Disponible en: https://www.ubu.es/vicerrectorado-de-investigacion-y-transferencia-del-conocimiento/comision-de-bioetica

481. Belmont I. Principios y guías éticos para la protección de los sujetos humanos de investigación. Com Nac Para Protección Los Sujetos Hum Investig Bioméd Comport USA. 1979;18.

482. de la Torre JC. How do heart disease and stroke become risk factors for Alzheimer's disease? Neurol Res. 1 de septiembre de 2006;28(6):637-44. Disponible en: https://doi.org/10.1179/016164106X130362

483. Zhou J, Yu JT, Wang HF, Meng XF, Tan CC, Wang J, et al. Association between Stroke and Alzheimer's Disease: Systematic review and meta-analysis. J Alzheimers Dis. 1 de enero de 2015;43(2):479-89. Disponible en: https://doi.org/10.3233/JAD-140666

484. Durazzo TC, Mattsson N, Weiner MW, Initiative ADN. Smoking and increased Alzheimer's disease risk: A review of potential mechanisms. Alzheimers Dement. 2014;10(3S): S122-45. Disponible en: https://doi.org/10.1016/j.jalz.2014.04.009

485. Merchant C, Tang MX, Albert S, Manly J, Stern Y, Mayeux R. The influence of smoking on the risk of Alzheimer's disease. Neurology. 1 de abril de 1999;52(7):1408-1408. Disponible en: https://doi.org/10.1212/WNL.52.7.1408

486. Ott A, Slooter A, Hofman A, van Harskamp F, Witteman J, Van Broeckhoven C, et al. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. The Lancet. 20 de junio de 1998;351(9119):1840-3. Disponible en: https://doi.org/10.1016/S0140-6736(97)07541-7

487. Thomas T, Thomas G, McLendon C, Sutton T, Mullan M. β-Amyloid-mediated vasoactivity and vascular endothelial damage. Nature. marzo de 1996;380(6570):168-71. Disponible en: https://doi.org/10.1038/380168a0

488. 2004 Surgeon General's Report: Consumer Summary | Smoking & Tobacco Use | CDC [Internet]. 2022 [citado 20 de diciembre de 2022]. Disponible en: https://www.cdc.gov/tobacco/sgr/2004/consumer_summary/index.htm

489. Reitz C, Heijer T den, Duijn C van, Hofman A, Breteler MMB. Relation between smoking and risk of dementia and Alzheimer disease: The Rotterdam Study. Neurology. 4 de septiembre de 2007;69(10):998-1005. Disponible en: https://doi.org/10.1212/01.wnl.0000271395.29695.9a

490. Reitz C, Luchsinger J, Tang MX, Mayeux R. Effect of smoking and time on cognitive function in the elderly without dementia. Neurology. 27 de septiembre de 2005;65(6):870-5. Disponible en: https://doi.org/10.1212/01.wnl.0000176057.22827.b7

491. Dobarro M, Gerenu G, Ramírez MJ. Propranolol reduces cognitive deficits, amyloid and tau pathology in Alzheimer's transgenic mice. Int J Neuropsychopharmacol. 1 de noviembre de 2013;16(10):2245-57. Disponible en: https://doi.org/10.1017/S1461145713000631

492. Dobarro M, Orejana L, Aguirre N, Ramírez MJ. Propranolol restores cognitive deficits and improves amyloid and Tau pathologies in a senescence-accelerated mouse model. Neuropharmacology. 1 de enero de 2013; 64:137-44. Disponible en: https://doi.org/10.1016/j.neuropharm.2012.06.047

493. Bergmann C, Sano M. Cardiac risk factors and potential treatments in Alzheimer's disease. Neurol Res. 1 de septiembre de 2006;28(6):595-604. Disponible en: https://doi.org/10.1179/016164106X130498

494. Holm H, Ricci F, Di Martino G, Bachus E, Nilsson ED, Ballerini P, et al. Beta-blocker therapy and risk of vascular dementia: A population-based prospective study. Vascul Pharmacol. 1 de febrero de 2020;125-126:106649. Disponible en: https://doi.org/10.1016/j.vph.2020.106649

495. Ramos BP, Arnsten AFT. Adrenergic pharmacology and cognition: Focus on the prefrontal cortex. Pharmacol Ther. 1 de marzo de 2007;113(3):523-36. Disponible en: https://doi.org/10.1016/j.pharmthera.2006.11.006

496. Brismar K, Mogensen L, Wetterberg L. Depressed melatonin secretion in patients with nightmares due to β-Adrenoceptor blocking drugs. Acta Med Scand. 1987;221(2):155-8. Disponible en: https://doi.org/10.1111/j.0954-6820.1987.tb01260.x

497. Brusco LI, Márquez M, Cardinali DP. Monozygotic twins with Alzheimer's disease treated with melatonin: Case report. J Pineal Res. 1998;25(4):260-3. Disponible en: https://doi.org/10.1111/j.1600-079X.1998.tb00396.x

498. Steinman MA, Zullo AR, Lee Y, Daiello LA, Boscardin WJ, Dore DD, et al. Association of β-blockers with functional outcomes, death, and rehospitalization in older nursing home residents after acute myocardial infarction. JAMA Intern Med. 1 de febrero de 2017;177(2):254-62. Disponible en: https://doi.org/10.1001/jamainternmed.2016.7701

499. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised intervention trial in-congestive heart failure (MERIT-HF). The Lancet. 12 de junio de 1999;353(9169):2001-7. Disponible en: https://doi.org/10.1016/S0140-6736(99)04440-2

500. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. agosto de 1991;325(5):293-302. Disponible en: https://doi.org/10.1056/NEJM199108013250501

501. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 6 de diciembre de 2001;345(23):1667-75. Disponible en: https://doi.org/10.1056/NEJMoa010713

502. Piazza-Gardner AK, Gaffud TJB, Barry AE. The impact of alcohol on Alzheimer's disease: A systematic review. Aging Ment Health. 1 de marzo de 2013;17(2):133-46. Disponible en: https://doi.org/10.1080/13607863.2012.742488

503. Bachman DL, Green RC, Benke KS, Cupples LA, Farrer LA. Comparison of Alzheimer's disease risk factors in white and African American families. Neurology. 22 de abril de 2003;60(8):1372-4. Disponible en: https://doi.org/10.1212/01.WNL.0000058751.43033.4D

504. Deng J, Zhou DHD, Li J, Wang YJ, Gao C, Chen M. A 2-year follow-up study of alcohol consumption and risk of dementia. Clin Neurol Neurosurg. 1 de junio de 2006;108(4):378-83. Disponible en: https://doi.org/10.1016/j.clineuro.2005.06.005

505. Ogunniyi A, Hall KS, Gureje O, Baiyewu O, Gao S, Unverzagt FW, et al. Risk factors for incident Alzheimer's disease in African Americans and Yoruba. Metab Brain Dis. 1 de septiembre de 2006;21(2):224-9. Disponible en: https://doi.org/10.1007/s11011-006-9017-2

506. Sparks DL, Martin TA, Gross DR, Hunsaker III JC. Link between heart disease, cholesterol, and Alzheimer's disease: A review. Microsc Res Tech. 2000;50(4):287-90. Disponible en: https://doi.org/10.1002/1097-0029(20000815)50:4<287: AID-JEMT7>3.0.CO;2-L

507. Kandel ER, Schwartz JH, Jessell TM, Siegelbaum S, Hudspeth AJ, Mack S. Principles of neural science. Vol. 4. McGraw-hill New York; 2000.

508. Tublin JM, Adelstein JM, del Monte F, Combs CK, Wold LE. Getting to the heart of Alzheimer Disease. Circ Res. 4 de enero de 2019;124(1):142-9. Disponible en: https://doi.org/10.1161/CIRCRESAHA.118.313563

509. Santiago JA, Potashkin JA. The Impact of disease comorbidities in Alzheimer's Disease. Front Aging Neurosci [Internet]. 2021 [citado 22 de diciembre de 2022];13. Disponible en: https://doi.org/10.3389/fnagi.2021.631770

510. Ostrovska S, Liholetov E, Pavlova V, Derkach A, Shevchenko I, Adegova L. Relationship between Alzheimer's disease, cerebrovascular and cardiovascular diseases

(literature review). Bull Probl Biol Med. :302-7. Disponible en: https://doi.org/10.29254/2077-4214-2021-1-159-302-307

511. Qiu C, Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. Nat Rev Cardiol. mayo de 2015;12(5):267-77. Disponible en: https://doi.org/10.1038/nrcardio.2014.223

512. Vernooij MW, Lugt A van der, Ikram MA, Wielopolski PA, Niessen WJ, Hofman A, et al. Prevalence and risk factors of cerebral microbleeds: The Rotterdam Scan Study. Neurology. 1 de abril de 2008;70(14):1208-14. Disponible en: https://doi.org/10.1212/01.wnl.0000307750.41970.d9

513. de Leeuw F -E., de Groot JC, Oudkerk M, Witteman JCM, Hofman A, van Gijn J, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. Brain. 1 de abril de 2002;125(4):765-72. Disponible en: https://doi.org/10.1093/brain/awf077

514. Petrovitch H, White LR, Izmirilian G, Ross GW, Havlik RJ, Markesbery W, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS☆. Neurobiol Aging. 1 de enero de 2000;21(1):57-62. Disponible en: https://doi.org/10.1016/S0197-4580(00)00106-8

515. Heijer T den, Launer LJ, Prins ND, Dijk EJ van, Vermeer SE, Hofman A, et al. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. Neurology. 25 de enero de 2005;64(2):263-7. Disponible en: https://doi.org/10.1212/01.WNL.0000149641.55751.2E

516. Korf ESC, White LR, Scheltens P, Launer LJ. Midlife blood pressure and the risk of hippocampal atrophy. hypertension. 2004;44(1):29-34. Disponible en: https://doi.org/10.1161/01.HYP.0000132475.32317.bb

517. Power MC, Weuve J, Gagne JJ, McQueen MB, Viswanathan A, Blacker D. The association between blood pressure and incident Alzheimer disease: a systematic review and

meta-analysis. Epidemiol Camb Mass. septiembre de 2011;22(5):646-59. Disponible en: https://doi.org/10.1097/EDE.0b013e31822708b5

518. O'Brien JT, Markus HS. Vascular risk factors and Alzheimer's disease. BMC Med. 11 de noviembre de 2014;12(1):218. Disponible en: https://doi.org/10.1186/s12916-014-0218-y

519. Takeda S, Rakugi H, Morishita R. Roles of vascular risk factors in the pathogenesis of dementia. Hypertens Res. marzo de 2020;43(3):162-7. Disponible en: https://doi.org/10.1038/s41440-019-0357-9

520. Hebert LE, Scherr PA, Beckett LA, Albert MS, Pilgrim DM, Chown MJ, et al. Age-specific incidence of Alzheimer's Disease in a community population. JAMA. 3 de mayo de 1995;273(17):1354-9. Disponible en: https://doi.org/10.1001/jama.1995.03520410048025

521. What causes Alzheimer's Disease? [Internet]. National Institute on Aging. [citado 1 de febrero de 2023]. Disponible en: https://www.nia.nih.gov/health/what-causes-alzheimers-disease

522. Rani A, Neha null, Sodhi RK, Kaur A. Protective effect of a calcium channel blocker «diltiazem» on aluminum chloride-induced dementia in mice. Naunyn Schmiedebergs Arch Pharmacol. noviembre de 2015;388(11):1151-61. Disponible en: https://doi.org/10.1007/s00210-015-1148-8

523. Anekonda TS, Quinn JF, Harris C, Frahler K, Wadsworth TL, Woltjer RL. L-type voltage-gated calcium channel blockade with isradipine as a therapeutic strategy for Alzheimer's disease. Neurobiol Dis. 1 de enero de 2011;41(1):62-70. Disponible en: https://doi.org/10.1016/j.nbd.2010.08.020

524. Wightman DP, Jansen IE, Savage JE, Shadrin AA, Bahrami S, Holland D, et al. A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease. Nat Genet. septiembre de 2021;53(9):1276-82. Disponible en: https://www.nature.com/articles/s41588-021-00921-z

525. Broce IJ, Tan CH, Fan CC, Jansen I, Savage JE, Witoelar A, et al. Dissecting the genetic relationship between cardiovascular risk factors and Alzheimer's disease. Acta Neuropathol (Berl). 1 de febrero de 2019;137(2):209-26. Disponible en: https://doi.org/10.1007/s00401-018-1928-6

526. Tang M, Maestre G, Tsai WY, Liu X, Feng L, Chung WY, et al. Effect of Age, Ethnicity, and head injury on the association between APOE genotypes and Alzheimer's Disease. 1996; 802:6-15. Disponible en: https://doi.org/10.1111/j.1749-6632.1996.tb32593.x

527. Mueller SG, Weiner MW. Selective effect of age, Apo e4, and Alzheimer's disease on hippocampal subfields. Hippocampus. 2009;19(6):558-64. Disponible en: https://doi.org/10.1002/hipo.20614

528. Calvó-Perxas L, Turró-Garriga O, Aguirregomozcorta M, Bisbe J, Hernández E, López-Pousa S, et al. Psychotropic drugs in patients with Alzheimer's Disease: A longitudinal study by the registry of dementias of Girona (ReDeGi) in Catalonia, Spain. J Am Med Dir Assoc. 1 de julio de 2014;15(7):497-503. Disponible en: https://doi.org/10.1016/j.jamda.2014.02.003

529. Taft LB, Barkin RL. Drug Abuse? Use and misuse of psychotropic drugs in Alzheimer's care. J Gerontol Nurs. agosto de 1990;16(8):4-9. Disponible en: https://doi.org/10.3928/0098-9134-19900801-04

530. Chang KJ, Hong CH, Lee Y, Lee KS, Roh HW, Back JH, et al. Effect of psychotropic drugs on development of Diabetes Mellitus in patients with Alzheimer's Disease. medicine (Baltimore). 12 de junio de 2015;94(23): e919. Disponible en: https://doi.org/10.1097/MD.0000000000000919

531. Becker RE, Seeman MV, Greig NH, Lahiri DK. What can triumphs and tribulations from drug research in Alzheimer's disease tell us about the development of psychotropic drugs in general? Lancet Psychiatry. 1 de agosto de 2015;2(8):756-64. Disponible en: https://doi.org/10.1016/S2215-0366(15)00214-X

532. Cummings JL. Cognitive and behavioral heterogeneity in Alzheimer's disease: seeking the neurobiological basis. Neurobiol Aging. 1 de noviembre de 2000;21(6):845-61. Disponible en: https://doi.org/10.1016/S0197-4580(00)00183-4

533. Weiner MF, Tractenberg RE, Sano M, Logsdon R, Teri L, Galasko D, et al. No long-term effect of behavioral treatment on psychotropic drug use for agitation in Alzheimer's Disease Patients. J Geriatr Psychiatry Neurol. 1 de junio de 2002;15(2):95-8. Disponible en: https://doi.org/10.1177/089198870201500208

534. Cancelli I, Valentinis L, Merlino G, Valente M, Gigli G. Drugs with anticholinergic properties as a risk factor for psychosis in patients affected by Alzheimer's Disease. Clin Pharmacol Ther. 2008;84(1):63-8. Disponible en: https://doi.org/10.1038/sj.clpt.6100435

535. Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's Disease: A review of 55 studies published from 1990 to 2003. Am J Psychiatry. noviembre de 2005;162(11):2022-30. Disponible en: https://doi.org/10.1176/appi.ajp.162.11.2022

536. Boccardi V, Murasecco I, Mecocci P. Diabetes drugs in the fight against Alzheimer's disease. Ageing Res Rev. 1 de septiembre de 2019; 54:100936. Disponible en: https://doi.org/10.1016/j.arr.2019.100936

537. Hölscher C. Diabetes as a risk factor for Alzheimer's disease: insulin signalling impairment in the brain as an alternative model of Alzheimer's disease. Biochem Soc Trans. 20 de julio de 2011;39(4):891-7. Disponible en: https://doi.org/10.1042/BST0390891

538. Lee PN. Smoking and Alzheimer's Disease: A Review of the epidemiological evidence. neuroepidemiology. 1994;13(4):131-44. Disponible en: https://doi.org/10.1159/000110372

539. Ritchie CW, Molinuevo JL, Truyen L, Satlin A, Van der Geyten S, Lovestone S. Development of interventions for the secondary prevention of Alzheimer's dementia: the european prevention of Alzheimer's Dementia (EPAD) project. Lancet Psychiatry. 1 de febrero de 2016;3(2):179-86. Disponible en: https://doi.org/10.1016/S2215-0366(15)00454-X

540. Prince M, Knapp M, Guerchet M, McCrone P, Prina M, Comas-Herrera M, et al. Dementia UK: update. 2014.

541. Wu YT, Fratiglioni L, Matthews FE, Lobo A, Breteler MMB, Skoog I, et al. Dementia in western Europe: epidemiological evidence and implications for policy making. Lancet Neurol. 1 de enero de 2016;15(1):116-24. Disponible en: https://doi.org/10.1016/S1474-4422(15)00092-7

542. Crous-Bou M, Minguillón C, Gramunt N, Molinuevo JL. Alzheimer's disease prevention: from risk factors to early intervention. Alzheimers Res Ther. 12 de septiembre de 2017;9(1):71. Disponible en: https://doi.org/10.1186/s13195-017-0297-z

543. Dhana K, Evans DA, Rajan KB, Bennett DA, Morris MC. Healthy lifestyle and the risk of Alzheimer dementia: Findings from 2 longitudinal studies. Neurology. 28 de julio de 2020;95(4): e374-83. Disponible en: https://doi.org/10.1212/WNL.0000000000009816

544. Langa KM. Is the risk of Alzheimer's Disease and dementia declining? Alzheimers Res Ther. 26 de marzo de 2015;7(1):34. Disponible en: https://doi.org/10.1186/s13195-015-0118-1

545. Ngandu T, Lehtisalo J, Korkki S, Solomon A, Coley N, Antikainen R, et al. The effect of adherence on cognition in a multidomain lifestyle intervention (FINGER). Alzheimers Dement. 2022;18(7):1325-34. Disponible en: https://doi.org/10.1002/alz.12492

546. Ferrante D, Virgolini M. Salud pública y factores de riesgo: vigilancia de factores de riesgo de enfermedades no transmisibles. Rev Argent Cardiol. 2005;73(3):221-7. Disponible en: https://www.redalyc.org/pdf/3053/305325329012.pdf

547. Kivipelto M, Mangialasche F. To what extent can Alzheimer disease be prevented? Nat Rev Neurol. octubre de 2014;10(10):552-3. Disponible en: https://doi.org/10.1038/nrneurol.2014.170

548. Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack CR, Jagust W, et al. Ways toward an early diagnosis in Alzheimer's disease: The Alzheimer's Disease Neuroimaging Initiative

(ADNI). Alzheimers Dement. 1 de julio de 2005;1(1):55-66. Disponible en: https://doi.org/10.1016/j.jalz.2005.06.003

549. San Miguel A, Rodríguez-Barbero MJ, San Miguel R, Alonso N, Calvo B, Martín-Gil FJ, et al. Estudio de marcadores biológicos en la Enfermedad de Alzheimer. Rev Electron BiomedElectron J Biomed. 2006; 1:88-99. Disponible en: https://www.researchgate.net/profile/Francisco-Javier-Martin-Gil/publication/26466207_Estudio_de_Marcadores_Diagnosticos_en_la_Enfermedad_de_Alzheimer/links/57eb86a108ae66664091f6fe/Estudio-de-Marcadores-Diagnosticos-en-la-Enfermedad-de-Alzheimer.pdf

550. Stone JG, Casadesus G, Gustaw-Rothenberg K, Siedlak SL, Wang X, Zhu X, et al. Frontiers in Alzheimer's disease therapeutics. Ther Adv Chronic Dis. 1 de enero de 2011;2(1):9-23. Disponible en: https://doi.org/10.1177/2040622310382817

551. Karin A, Hannesdottir K, Jaeger J, Annas P, Segerdahl M, Karlsson P, et al. Psychometric evaluation of ADAS-Cog and NTB for measuring drug response. Acta Neurol Scand. 2014;129(2):114-22. Disponible en: https://doi.org/10.1111/ane.12153

552. Nitrini R. Preclinical diagnosis of Alzheimer's disease: ¿Prevention or prediction? Dement Neuropsychol. diciembre de 2010; 4:259-61. Disponible en: https://doi.org/10.1590/S1980-57642010DN40400002

553. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener. 2 de agosto de 2019;14(1):32. Disponible en: https://doi.org/10.1186/s13024-019-0333-5

554. Jobe JB, Smith DM, Ball K, Tennstedt SL, Marsiske M, Willis SL, et al. Active: A cognitive intervention trial to promote independence in older adults. Control Clin Trials. 1 de agosto de 2001;22(4):453-79. Disponible en: https://doi.org/10.1016/S0197-2456(01)00139-8

555. Edwards JD, Xu H, Clark D, Ross LA, Unverzagt FW. S2-01-02: The active study: What we have learned and what is next? Cognitive training reduces incident dementia across ten years. Alzheimers Dement. 2016;12(7S_Part_4): P212-P212. Disponible en: https://doi.org/10.1016/j.jalz.2016.06.373

556. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol. 1 de mayo de 2017;16(5):377-89. Disponible en: https://doi.org/10.1016/S1474-4422(17)30040-6

557. Richard E, den Heuvel EV, Moll van Charante EP, Achthoven L, Vermeulen M, Bindels PJ, et al. Prevention of Dementia by Intensive Vascular Care (PreDIVA): A Cluster-randomized trial in progress. Alzheimer Dis Assoc Disord. septiembre de 2009;23(3):198. Disponible en: https://doi.org/10.1097/WAD.0b013e31819783a4

558. van Charante EPM, Richard E, Eurelings LS, van Dalen JW, Ligthart SA, van Bussel EF, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. The Lancet. 20 de agosto de 2016;388(10046):797-805. Disponible en: https://doi.org/10.1016/S0140-6736(16)30950-3

559. Sexton C, Solis M, Aharon-Peretz J, Alexopoulos P, Apostolova LG, Bayen E, et al. Alzheimer's disease research progress in the Mediterranean region: The Alzheimer's Association International Conference Satellite Symposium. Alzheimers Dement. 2022;18(10):1957-68. Disponible en: https://doi.org/10.1002/alz.12588

560. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martínez-González MÁ, et al. Mediterranean diet and age-related cognitive decline: A Randomized clinical Trial. JAMA Intern Med. 1 de julio de 2015;175(7):1094-103. Disponible en: https://doi.org/10.1001/jamainternmed.2015.1668

561. Margolles Martins M. Más allá de la clínica. La vigilancia epidemiológica. FormActPediatr Aten Prim. 2010; 8 (3): 35-42. [acceso 09/02/2021];(3): 35-42.

562. Rodriguez J, Gajardo J. Sobre la contribución de la Terapia Ocupacional en el manejo no farmacológico de los síntomas psicológicos y conductuales asociados a la demencia. Rev Chil Ter Ocupacional [Internet]. 7 de diciembre de 2012 [citado 19 de febrero de 2023];12(2). Disponible en: https://doi.org/10.5354/0719-5346.2012.25307

563. Zhou Z, Liang Y, Zhang X, Xu J, Lin J, Zhang R, et al. low-density lipoprotein cholesterol and Alzheimer's Disease: A systematic review and meta-analysis. Front Aging Neurosci. 2020; 12:5. Disponible en: https://doi.org/10.3389/fnagi.2020.00005

564. Ban Y, Watanabe T, Suguro T, Matsuyama T aki, Iso Y, Sakai T, et al. Increased plasma urotensin-II and carotid atherosclerosis are associated with vascular dementia. J Atheroscler Thromb. 2009;16(3):179-87. Disponible en: https://doi.org/10.5551/jat.E608

565. Cacabelos R, Ferna\' ndez-Novoa L, Lombardi V, Corzo L, Pichel V, Kubota Y. Cerebrovascular risk factors in Alzheimer's disease: brain hemodynamics and pharmacogenomic implications. Neurol Res. 2003;25(6):567-80. Disponible en: https://doi.org/10.1179/016164103101202002

566. Caramelli P, Nitrini R, Maranhao R, Lourenço ACG, Damasceno MC, Vinagre C, et al. Increased apolipoprotein B serum concentration in Alzheimer's disease. Acta Neurol Scand. 1999;100(1):61-3. Disponible en: https://doi.org/10.1111/j.1600-0404.1999.tb00724.x

567. Chen H, Du Y, Liu S, Ge B, Ji Y, Huang G. Association between serum cholesterol levels and Alzheimer's disease in China: A case-control study. Int J Food Sci Nutr. 2019;70(4):405-11. Disponible en: https://doi.org/10.1080/09637486.2018.1508426

568. Hoshino T, Kamino K, Matsumoto M. Gene dose effect of the APOE-ϵ4 allele on plasma HDL cholesterol level in patients with Alzheimer's disease. Neurobiol Aging. 2002;23(1):41-5. Disponible en: https://doi.org/10.1016/S0197-4580(01)00252-4

569. Kouzuki M, Nagano M, Suzuki T, Katsumata Y, Nakamura S, Takamura A, et al. Cerebrospinal fluid biomarkers of Alzheimer's disease are associated with carotid plaque score and hemodynamics in intra-and extra-cranial arteries on ultrasonography. J Clin Neurosci. 2018; 49:32-6. Disponible en: https://doi.org/10.1016/j.jocn.2017.12.006

570. Kuo YM, Emmerling MR, Bisgaier CL, Essenburg AD, Lampert HC, Drumm D, et al. Elevated low-density lipoprotein in Alzheimer's disease correlates with brain Aβ 1-42 levels. Biochem Biophys Res Commun. 1998;252(3):711-5. Disponible en: https://doi.org/10.1006/bbrc.1998.9652

571. Lehtonen A, Luutonen S. High-density lipoprotein cholesterol levels of very old people in the diagnosis of dementia. Age Ageing. 1 de septiembre de 1986;15(5):267-70. Disponible en: https://doi.org/10.1093/ageing/15.5.267

572. Lesser G, Kandiah K, Libow LS, Likourezos A, Breuer B, Marin D, et al. Elevated serum total and LDL cholesterol in very old patients with Alzheimer's disease. Dement Geriatr Cogn Disord. 2001;12(2):138-45. Disponible en: https://doi.org/10.1159/000051248

573. Macesic M, M Lalic N, S Kostic V, Jotic A, Lalic K, Stefanova E, et al. Impaired insulin sensitivity and secretion in patients with Alzheimer's disease: the relationship with other atherosclerosis risk factors. Curr Vasc Pharmacol. 2017;15(2):158-66. Disponible en: https://doi.org/10.2174/1570161114666160905170644

574. Mamo JCL, Jian L, James AP, Flicker L, Esselmann H, Wiltfang J. Plasma lipoprotein β-amyloid in subjects with Alzheimer's disease or mild cognitive impairment. Ann Clin Biochem. 2008;45(4):395-403. Disponible en: https://doi.org/10.1258/acb.2008.007214

575. Moroney JT, Tang MX, Berglund L, Small S, Merchant C, Bell K, et al. Low-density lipoprotein cholesterol and the risk of dementia with stroke. Jama. 1999;282(3):254-60. Disponible en: https://doi.org/10.1001/jama.282.3.254

576. Panza F, Solfrizzi V, Colacicco AM, Basile AM, D'Introno A, Capurso C, et al. Apolipoprotein E (APOE) polymorphism influences serum APOE levels in Alzheimer's

disease patients and centenarians. Neuroreport. 2003;14(4):605-8. Disponible en: https://doi.org/10.1097/00001756-200303240-00016

577. Paragh G, Balla P, Katona E, Seres I, Égerházi A, Degrell I. Serum paraoxonase activity changes in patients with Alzheimer's disease and vascular dementia. Eur Arch Psychiatry Clin Neurosci. 2002;252(2):63-7. Disponible en: https://doi.org/10.1007/s004060200013

578. Reitz C, Tang MX, Luchsinger J, Mayeux R. Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch Neurol. 2004;61(5):705-14. Disponible en: https://doi.org/10.1001/archneur.61.5.705

579. Ryglewicz D, Rodo M, Kunicki PK, Bednarska-Makaruk M, Graban A, Lojkowska W, et al. Plasma antioxidant activity and vascular dementia. J Neurol Sci. 2002; 203:195-7. Disponible en: https://doi.org/10.1016/S0022-510X(02)00290-3

580. Scacchi R, De Bernardini L, Mantuano E, Vilardo T, Donini LM, Ruggeri M, et al. DNA polymorphisms of apolipoprotein B and angiotensin I-converting enzyme genes and relationships with lipid levels in Italian patients with vascular dementia or Alzheimer's disease. Dement Geriatr Cogn Disord. 1998;9(4):186-90. Disponible en: https://doi.org/10.1159/000017045

581. Shafagoj YA, Naffa RG, El-Khateeb MS, Abdulla YL, Al-Qaddoumi AA, Khatib FA, et al. APOE Gene polymorphism among Jordanian Alzheimer's patients with relation to lipid profile. Neurosciences. 2018;23(1):29-34. Disponible en: https://doi.org/10.17712/nsj.2018.1.20170169

582. Solfrizzi V, Panza F, D'introno A, Colacicco AM, Capurso C, Basile AM, et al. Lipoprotein (a), apolipoprotein E genotype, and risk of Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2002;72(6):732-6. Disponible en: https://doi.org/10.1136/jnnp.72.6.732

583. Tang Y, Li YM, Zhang M, Chen YQ, Sun Q. ε3/4 genotype of the apolipoprotein E is associated with higher risk of Alzheimer's disease in patients with type 2 diabetes mellitus. Gene. 2019; 703:65-70. Disponible en: https://doi.org/10.1016/j.gene.2019.03.024

584. Warren MW, Hynan LS, Weiner MF. Lipids and adipokines as risk factors for Alzheimer's disease. J Alzheimers Dis. 2012;29(1):151-7. Disponible en: https://doi.org/10.3233/JAD-2012-111385

585. Watanabe T, Miyazaki A, Katagiri T, Yamamoto H, Idei T, Iguchi T. Relationship between serum insulin-like growth factor-1 levels and Alzheimer's disease and vascular dementia. J Am Geriatr Soc. 2005;53(10):1748-53. Disponible en: https://doi.org/10.1111/j.1532-5415.2005.53524.x

586. Wehr H, Bednarska-Makaruk M, \Lojkowska W, Graban A, Hoffman-Zacharska D, Kuczyńska-Zardzewia\ly A, et al. Differences in risk factors for dementia with neurodegenerative traits and for vascular dementia. Dement Geriatr Cogn Disord. 2006;22(1):1-7. Disponible en: https://doi.org/10.1159/000092845

587. Wolf H, Hensel A, Arendt T, Kivipelto M, Winblad B, Gertz HJ. Serum lipids and hippocampal volume: the link to Alzheimer's disease? Ann Neurol Off J Am Neurol Assoc Child Neurol Soc. 2004;56(5):745-9. Disponible en: https://doi.org/10.1002/ana.20289

588. Yamamoto H, Watanabe T, Miyazaki A, Katagiri T, Idei T, Iguchi T, et al. High prevalence of chlamydia pneumoniae antibodies and increased high-sensitive c-reactive protein in patients with vascular dementia. J Am Geriatr Soc. 2005;53(4):583-9. Disponible en: https://doi.org/10.1111/j.1532-5415.2005.53204.x

589. Yavuz BB, Yavuz B, Halil M, Cankurtaran M, Ulger Z, Cankurtaran ES, et al. Serum elevated gamma glutamyltransferase levels may be a marker for oxidative stress in Alzheimer's disease. Int Psychogeriatr. agosto de 2008;20(4):815-23. Disponible en: https://doi.org/10.1017/S1041610208006790

590. Liu Y, Zhong X, Shen J, Jiao L, Tong J, Zhao W, et al. Elevated serum TC and LDL-C levels in Alzheimer's disease and mild cognitive impairment: A meta-analysis study. Brain Res. 2020; 1727:146554. Disponible en: https://doi.org/10.1016/j.brainres.2019.146554

591. Kalman J, Kudchodkar BJ, Murray K, McConathy WJ, Juhasz A, Janka Z, et al. Evaluation of serum-lipid-related cardiovascular risk factors in Alzheimer's disease. Dement Geriatr Cogn Disord. 1999;10(6):488-93. Disponible en: https://doi.org/10.1159/000017195

592. Merched A, Xia Y, Visvikis S, Serot JM, Siest G. Decreased high-density lipoprotein cholesterol and serum apolipoprotein AI concentrations are highly correlated with the severity of Alzheimer's disease☆. Neurobiol Aging. 1 de enero de 2000;21(1):27-30. Disponible en: https://doi.org/10.1016/S0197-4580(99)00103-7

593. Lesser GT, Haroutunian V, Purohit DP, Beeri MS, Schmeidler J, Honkanen L, et al. Serum lipids are related to Alzheimer's pathology in nursing home residents. Dement Geriatr Cogn Disord. 2009;27(1):42-9. Disponible en: https://doi.org/10.1159/000189268

594. Sun X, Shao H, Yu D, Wang D. Analysis of correlation between insulin resistance, blood lipids and Alzheimer's disease. Wei Sheng Yan Jiu. 2010;39(5):573-5. Disponible en: https://europepmc.org/article/med/21033433

595. Presečki P, Mück-Šeler D, Mimica N, Pivac N, Mustapić M, Stipčević T, et al. Serum lipid levels in patients with Alzheimer's disease. Coll Antropol. 2011;35(1):115-20. Disponible en: https://hrcak.srce.hr/64053

596. Parnowski T, Ka\luza B. Metabolic syndrome and cognitive dysfunction in the old age. Psychiatr Pol. 2013;47(6):1087-99. Disponible en: https://europepmc.org/article/med/25007540

597. Grossi MF, Carvalho M das G, Silveira JN, Gonçalves GS, Gomes KB, Bicalho MA, et al. OxLDL plasma levels in patients with Alzheimer's disease. Arq Neuropsiquiatr. 2018;76(4):241-6. Disponible en: https://doi.org/10.1590/0004-282x20180012

598. Wu Y, Wang Z, Jia X, Zhang H, Zhang H, Li J, et al. Prediction of Alzheimer's disease with serum lipid levels in Asian individuals: a meta-analysis. Biomarkers. 19 de mayo de 2019;24(4):341-51. Disponible en: https://doi.org/10.1080/1354750X.2019.1571633

599. Agarwal R, Talwar P, Kushwaha SS, Tripathi CB, Kukreti R. Effect of apolipoprotein E (APO E) polymorphism on leptin in Alzheimer's disease. Ann Indian Acad Neurol. 2015;18(3):320. Disponible en: https://doi.org/10.4103/0972-2327.157255

600. Alam R, Tripathi M, Mansoori N, Parveen S, Luthra K, Lakshmy R, et al. Synergistic epistasis of paraoxonase 1 (rs662 and rs85460) and apolipoprotein E4 genes in pathogenesis of Alzheimer's disease and vascular dementia. Am J Alzheimers Dis Dementias®. 2014;29(8):769-76. Disponible en: https://doi.org/10.1177/1533317514539541

601. Cankurtaran M, Yavuz BB, Halil M, Dagli N, Cankurtaran ES, Ariogul S. Are serum lipid and lipoprotein levels related to dementia? Arch Gerontol Geriatr. 2005;41(1):31-9. Disponible en: https://doi.org/10.1016/j.archger.2004.10.008

602. Chang L, Wang Y, Ji H, Dai D, Xu X, Jiang D, et al. Elevation of peripheral BDNF promoter methylation links to the risk of Alzheimer's disease. PloS One. 2014;9(11). Disponible en: https://doi.org/10.1371/journal.pone.0110773

603. Duan D, Ling Y, Zhou Y. A clinical study on the serum triglyceride and total cholesterol of patients with vascular dementia and Alzheimer's disease. Chin J Prev Control Chronic Dis. 2006;(02). Disponible en: https://pesquisa.bvsalud.org/portal/resource/pt/wpr-532104

604. Han, J.F. Correlation between the levels of serum lipids and the onset of disease in patients with Alzheimer's disease. Chinese Journal of Clinical Rehabilitation. 2005;21. Disponible en: https://www.researchgate.net/publication/289458835_Correlation_between_the_levels_of_serum_lipids_and_the_onset_of_disease_in_patients_with_Alzheimer_disease_11_paired_observation

605. Li, W. Relationship between changes of blood lipid metabolism and disease in patients with Alzheimer's disease. Medical Information. 2014;27.

606. Liu JH, Chen ZL. Observation of serum cholesterol IL-6 and VitB12 levels in Alzheimer's disease or vascular dementia patients. J Jiangsu Univ Med Ed. 2006;16(1):48-50.

607. Liu, Z.S. Study of lipid metabolism in patients with sporadic Alzheimer's disease. China J Nerv Ment Dis. 2005;31. Disponible en: https://link.springer.com/article/10.1007/s12264-013-1410-3

608. Raygani AV, Rahimi Z, Kharazi H, Tavilani H, Pourmotabbed T. Association between apolipoprotein E polymorphism and serum lipid and apolipoprotein levels with Alzheimer's disease. Neurosci Lett. 2006;408(1):68-72. Disponible en: https://doi.org/10.1016/j.neulet.2006.08.048

609. Shim, Y.S. Elevated remnant lipoprotein cholesterol in patients with Alzheimer's disease and vascular dementia: a pilot study. Dementia and Neurocognitive Disorders. 2010;7.

610. Singh NK, Chhillar N, Banerjee BD, Bala K, Mukherjee AK, Mustafa MD, et al. Gene-environment interaction in Alzheimer's disease. Am J Alzheimers Dis Dementias. 2012;27(7):496-503. Disponible en: https://doi.org/10.1177/1533317512456067

611. Sun, Y.L. Observation of blood lipid levels in patients with Alzheimer's disease. China J Misdiagn. 2006;23.

612. Vasantharekha R, Priyanka HP, Swarnalingam T, Srinivasan AV, ThyagaRajan S. Interrelationship between Mini-Mental State Examination scores and biochemical parameters in patients with mild cognitive impairment and Alzheimer's disease. Geriatr Gerontol Int. 2017;17(10):1737-45. Disponible en: https://doi.org/10.1111/ggi.12957

613. Wada H. Analyses of serum concentrations of apolipoproteins in the demented elderly. Intern Med. 2000;39(3):220-2. Disponible en: https://doi.org/10.2169/internalmedicine.39.220

614. Wang CY. A clinical study of Alzheimer's disease and vascular dementia in serum cholesterol, Vit B12, and folate acid. Chinese Journal of Nervous and mental disease. 2005.

615. Wang H. Study on the combining assay of total antioxidant status, high sensitive Creactive protein and serum lipids in the diagnosis of Alzheimer's disease. Laboratory Medicine. 2006;21.

616. Wang R., Chen Z, Fu Y, Wei X, Liao J, Liu X et al. Plasma cystatin c and high-density lipoprotein are important biomarkers of Alzheimer's disease and vascular dementia: a cross-sectional study. Frontiers in aging neuroscience. 2017;9. Disponible en: https://doi.org/10.3389/fnagi.2017.00026

617. Wang X.H. Changes of serum levels of thyroid hormones and blood lipid in patients with varying degrees of Alzheimer's disease and related risk factors. Journal of Clinical Medicine in Practice. 2016;4. Disponible en:

618. Watanabe T, Koba S, Kawamura M, Itokawa M, Idei T, Nakagawa Y, et al. Small dense low-density lipoprotein and carotid atherosclerosis in relation to vascular dementia. Metabolism. 2004;53(4):476-82. Disponible en: https://doi.org/10.1016/j.metabol.2003.11.020

619. Xiao Z, Wang J, Chen W, Wang P, Zeng H, Chen W. Association studies of several cholesterol-related genes (ABCA1, CETP and LIPC) with serum lipids and risk of Alzheimer's disease. Lipids Health Dis. 2012;11(1):163. Disponible en: https://doi.org/10.1186/1476-511X-11-163

620. Xiaohong W, Shuyun Z, Xiaozhong Y. Relationship between lipid disorders and carotid artery atherosclerosis. Mod J Integr Tradit Chin West Med. 2010;17.

621. Yang, CZ, Tian JZ, Zhong J. Changes of blood lipid in mild cognitive impairment and Alzheimer's disease. Chinese Journal of Gerontology. 2007;4.

622. Yu Z, Li W, Hou D, Zhou L, Deng Y, Tian M, et al. Relationship between adiponectin gene polymorphisms and late-onset Alzheimer's disease. PloS One. 2015;10(4). Disponible en: https://doi.org/10.1371/journal.pone.0125186

623. Yuan YG, Ye Q, Chen Y, Li HL, Lu R, Mei G, et al. A study of serum lipid concentrations and apolipoprotein E genotype among patients with senile depression and alzhemier disease. Chin Gen Pract. 2006;9:106-8.

624. Yue YH. Analysis of low density lipoprotein receptor-related protein gene 766C/T polymorphism and the levels of serum lipids in patients with Alzheimer's disease in Xinjiang Uygurs. China J Psychiatry. 2009;42.

625. Zengi O, Karakas A, Ergun U, Senes M, Inan L, Yucel D. Urinary 8-hydroxy-2'-deoxyguanosine level and plasma paraoxonase 1 activity with Alzheimer's disease. Clin Chem Lab Med. 2012;50(3):529-34. https://doi.org/10.1515/cclm.2011.792

626. Zhao Z, Zhou H, Peng Y, Qiu CH, Sun QY, Wang F, et al. Expression and significance of plasma 3-NT and ox-LDL in patients with Alzheimer's. Genet Mol Res. 2014;13(4):8428-35. Disponible en: https://doi.org/10.4238/2014.October.20.19

627. Zheng J, Yan H, Shi L, Kong Y, Zhao Y, Xie L, et al. The CYP19A1 rs3751592 variant confers susceptibility to Alzheimer disease in the Chinese Han population. Medicine (Baltimore). 2016;95(35). Disponible en: https://doi.org/10.1097/MD.0000000000004742

628. Zhong X, Yinglan LI, Can DU, Guofeng LI, Hongjuan LI, Zhu A. Changes in serum homocysteine and its correlation with altitude, folacin and high-sensitivity C-reactive protein in Tibetan patients with mild-to-moderate Alzheimer's disease at different altitudes. Chin J Geriatr. 2016;35(9):934-8. Disponible en: https://pesquisa.bvsalud.org/portal/resource/pt/wpr-502427

629. Zhou TT. Comparative study on serum inflammatory cytokines and blood lipids in Alzheimer's disease and varcular dementia. Medical Journal of Chinese People's Health. 2015;2.

630. Zhu JY. Comparison of serum lipids, serum CRP, Hcy and sIL-6R in patients with Alzheimer's disease and those of the same age. Pract Geriatr. 2007;21.

631. Wang HL, Wang YY, Liu XG, Kuo SH, Liu N, Song QY, et al. Cholesterol, 24-hydroxycholesterol, and 27-hydroxycholesterol as surrogate biomarkers in cerebrospinal fluid in mild cognitive impairment and alzheimer's disease: a meta-analysis. J Alzheimers Dis. 1 de enero de 2016;51(1):45-55. Disponible en: https://doi.org/10.3233/JAD-150734

632. Papassotiropoulos A, Lütjohann D, Bagli M, Locatelli S, Jessen F, Buschfort R, et al. 24S-hydroxycholesterol in cerebrospinal fluid is elevated in early stages of dementia. J Psychiatr Res. 2002;36(1):27-32. Disponible en: https://doi.org/10.1016/S0022-3956(01)00050-4

633. Martínez-Morillo E, Hansson O, Atagi Y, Bu G, Minthon L, Diamandis EP, et al. Total apolipoprotein E levels and specific isoform composition in cerebrospinal fluid and plasma from Alzheimer's disease patients and controls. Acta Neuropathol (Berl). 2014;127(5):633-43. Disponible en: https://doi.org/10.1007/s00401-014-1266-2

634. Kölsch H, Lütjohann D, Jessen F, Urbach H, Von Bergmann K, Maier W, et al. Polymorphism in neuropeptide Y influences CSF cholesterol levels but is no major risk factor of Alzheimer's disease. J Neural Transm. 2006;113(2):231-8. Disponible en: https://doi.org/10.1007/s00702-005-0319-z

635. Kölsch H, Lütjohann D, Jessen F, Popp J, Hentschel F, Kelemen P, et al. CYP46A1 variants influence Alzheimer's disease risk and brain cholesterol metabolism. Eur Psychiatry. 2009;24(3):183-90. Disponible en: https://doi.org/10.1016/j.eurpsy.2008.12.005

636. Kölsch H, Lütjohann D, Jessen F, Popp J, Hentschel F, Kelemen P, et al. RXRA gene variations influence Alzheimer's disease risk and cholesterol metabolism. J Cell Mol Med. 2009;13(3):589-98. Disponible en: https://doi.org/10.1111/j.1582-4934.2009.00383.x

637. Kölsch H, Heun R, Jessen F, Popp J, Hentschel F, Maier W, et al. Alterations of cholesterol precursor levels in Alzheimer's disease. Biochim Biophys Acta BBA - Mol Cell

Biol Lipids. 1 de agosto de 2010;1801(8):945-50. Disponible en: https://doi.org/10.1016/j.bbalip.2010.03.001

638. Qureischie H, Heun R, Lütjohann D, Popp J, Jessen F, Ledschbor-Frahnert C, et al. CETP polymorphisms influence cholesterol metabolism but not Alzheimer's disease risk. Brain Res. 26 de septiembre de 2008; 1232:1-6. Disponible en: https://doi.org/10.1016/j.brainres.2008.07.047

639. Mateos L, Ismail MAM, Gil-Bea FJ, Leoni V, Winblad B, Björkhem I, et al. Upregulation of Brain Renin Angiotensin System by 27-Hydroxycholesterol in Alzheimer's Disease. J Alzheimers Dis. 1 de enero de 2011;24(4):669-79. Disponible en: https://doi.org/10.3233/JAD-2011-101512

640. Wollmer MA, Streffer JR, Tsolaki M, Grimaldi LME, Lütjohann D, Thal D, et al. Genetic association of acyl-coenzyme A: cholesterol acyltransferase with cerebrospinal fluid cholesterol levels, brain amyloid load, and risk for Alzheimer's disease. Mol Psychiatry. junio de 2003;8(6):635-8. Disponible en: https://doi.org/10.1038/sj.mp.4001296

641. Wollmer MA, Streffer JR, Lütjohann D, Tsolaki M, Iakovidou V, Hegi T, et al. ABCA1 modulates CSF cholesterol levels and influences the age at onset of Alzheimer's disease. Neurobiol Aging. 1 de mayo de 2003;24(3):421-6. Disponible en: https://doi.org/10.1016/S0197-4580(02)00094-5

642. Shafaati M, Solomon A, Kivipelto M, Björkhem I, Leoni V. Levels of ApoE in cerebrospinal fluid are correlated with Tau and 24S-hydroxycholesterol in patients with cognitive disorders. Neurosci Lett. 25 de septiembre de 2007;425(2):78-82. Disponible en: https://doi.org/10.1016/j.neulet.2007.08.014

643. Schönknecht P, Lütjohann D, Pantel J, Bardenheuer H, Hartmann T, von Bergmann K, et al. Cerebrospinal fluid 24S-hydroxycholesterol is increased in patients with Alzheimer's disease compared to healthy controls. Neurosci Lett. 10 de mayo de 2002;324(1):83-5. Disponible en: https://doi.org/10.1016/S0304-3940(02)00164-7

644. Popp J, Lewczuk P, Kölsch H, Meichsner S, Maier W, Kornhuber J, et al. Cholesterol metabolism is associated with soluble amyloid precursor protein production in Alzheimer's disease. J Neurochem. 2012;123(2):310-6. Disponible en: https://doi.org/10.1111/j.1471-4159.2012.07893.x

645. Popp J, Meichsner S, Kölsch H, Lewczuk P, Maier W, Kornhuber J, et al. Cerebral and extracerebral cholesterol metabolism and CSF markers of Alzheimer's disease. Biochem Pharmacol. 1 de julio de 2013;86(1):37-42. Disponible en: https://doi.org/10.1016/j.bcp.2012.12.007

646. Vanmierlo T, Popp J, Kölsch H, Friedrichs S, Jessen F, Stoffel-Wagner B, et al. The plant sterol brassicasterol as additional CSF biomarker in Alzheimer's disease. Acta Psychiatr Scand. 2011;124(3):184-92. Disponible en: https://doi.org/10.1111/j.1600-0447.2011.01713.x

647. Leoni V, Caccia C. Potential diagnostic applications of side chain oxysterols analysis in plasma and cerebrospinal fluid. Biochem Pharmacol. 2013;86(1):26-36. Disponible en: https://doi.org/10.1016/j.bcp.2013.03.015

648. Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2015;86(12):1299-306. Disponible en: https://doi.org/10.1136/jnnp-2015-310548

649. Tan ZS, Seshadri S, Beiser A, Wilson PW, Kiel DP, Tocco M, et al. Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham Study. Arch Intern Med. 2003;163(9):1053-7. Disponible en: https://doi.org/10.1001/archinte.163.9.1053

650. Li G, Shofer JB, Kukull WA, Peskind ER, Tsuang DW, Breitner JC, et al. Serum cholesterol and risk of Alzheimer disease: a community-based cohort study. Neurology. 2005;65(7):1045-50. Disponible en: https://doi.org/10.1212/01.wnl.0000178989.87072.11

651. Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. Dement Geriatr Cogn Disord. 2009;28(1):75-80. Disponible en: https://doi.org/10.1159/000231980

652. Mielke MM, Zandi PP, Shao H, Waern M, Östling S, Guo X, et al. The 32-year relationship between cholesterol and dementia from midlife to late life. Neurology. 2010;75(21):1888-95. Disponible en: https://doi.org/10.1212/WNL.0b013e3181feb2bf

653. Huang CC, Chung CM, Leu HB, Lin LY, Chiu CC, Hsu CY, et al. Diabetes mellitus and the risk of Alzheimer's disease: a nationwide population-based study. PloS One. 2014;9(1). Disponible en: https://doi.org/10.1371/journal.pone.0087095

654. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, K\aareholt I, Winblad B, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol. 2005;62(10):1556-60. Disponible en: https://doi.org/10.1001/archneur.62.10.1556

655. Reitz C, Tang MX, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Association of higher levels of high-density lipoprotein cholesterol in elderly individuals and lower risk of late-onset Alzheimer disease. Arch Neurol. 2010;67(12):1491-7. Disponible en: https://doi.org/10.1001/archneurol.2010.297

656. Kimm H, Lee PH, Shin YJ, Park KS, Jo J, Lee Y, et al. Mid-life and late-life vascular risk factors and dementia in Korean men and women. Arch Gerontol Geriatr. 2011;52(3): e117-22. Disponible en: https://doi.org/10.1016/j.archger.2010.09.004

657. Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, et al. Apolipoprotein E ϵ4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med. 2002;137(3):149-55. Disponible en: https://doi.org/10.7326/0003-4819-137-3-200208060-00006

658. Hayden KM, Zandi PP, Lyketsos CG, Khachaturian AS, Bastian LA, Charoonruk G, et al. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. Alzheimer Dis Assoc Disord. 2006;20(2):93-100. Disponible en: https://doi.org/10.1097/01.wad.0000213814.43047.86

659. Notkola IL, Sulkava R, Pekkanen J, Erkinjuntti T, Ehnholm C, Kivinen P, et al. Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. Neuroepidemiology. 1998; 17:14-20. Disponible en: https://doi.org/10.1159/000026149

660. Rönnemaa E, Zethelius B, Lannfelt L, Kilander L. Vascular risk factors and dementia: 40-year follow-up of a population-based cohort. Dement Geriatr Cogn Disord. 2011;31(6):460-6. Disponible en: https://doi.org/10.1159/000330020

661. Wang KC, Woung LC, Tsai MT, Liu CC, Su YH, Li CY. Risk of Alzheimer's disease in relation to diabetes: a population-based cohort study. Neuroepidemiology. 2012;38(4):237-44. Disponible en: https://doi.org/10.1159/000337428

662. Lieb W, Beiser AS, Vasan RS, Tan ZS, Au R, Harris TB, et al. Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. JAMA. 2009; 302:2565-2572. Disponible en: https://doi.org/10.1001/jama.2009.1836

663. Dal Forno G, Palermo MT, Donohue JE, Karagiozis H, Zonderman AB, Kawas CH. Depressive symptoms, sex, and risk for Alzheimer's disease. Ann Neurol. 2005;57(3):381-7. Disponible en: https://doi.org/10.1002/ana.20405

664. Forti P, Pisacane N, Rietti E, Lucicesare A, Olivelli V, Mariani E, et al. Metabolic syndrome and risk of dementia in older adults. J Am Geriatr Soc. 2010;58(3):487-92. Disponible en: https://doi.org/10.1111/j.1532-5415.2010.02731.x

665. Raffaitin C, Gin H, Empana JP, Helmer C, Berr C, Tzourio C, et al. Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: the Three-City Study. Diabetes Care. 2009;32(1):169-74. Disponible en: https://doi.org/10.2337/dc08-0272

666. Muller M, Tang MX, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Metabolic syndrome and dementia risk in a multiethnic elderly cohort. Dement Geriatr Cogn Disord. 2007;24(3):185-92. Disponible en: https://doi.org/10.1159/000105927

667. Lehtonen A, Luutonen S. High-density lipoprotein cholesterol levels of very old people in the diagnosis of dementia. Age Ageing. 1986;15(5):267-70. Disponible en: https://doi.org/10.1093/ageing/15.5.267

668. Leoni V, Solomon A, Lövgren-Sandblom A, Minthon L, Blennow K, Hansson O et al. Diagnostic power of 24s-hydroxycholesterol in cerebrospinal fluid: candidate marker of brain health - IOS Press. 2013; 36 (4): 739-747. [Internet]. [citado 18 de abril de 2020]. Disponible en: https://content.iospress.com/articles/journal-of-alzheimers-disease/jad130035

669. Gabin JM, Tambs K, Saltvedt I, Sund E, Holmen J. Association between blood pressure and Alzheimer disease measured up to 27 years prior to diagnosis: the HUNT Study. Alzheimers Res Ther. 2017;9(1):1-12. Disponible en: https://doi.org/10.1186/s13195-017-0262-x

670. Li G, Shen Y, Li Y, Chen C, Zhau Y, Silverman J. A case-control study of Alzheimer's disease in China. Neurology. 1992;42(8):1481-1481. Disponible en: https://doi.org/10.1212/WNL.42.8.1481

671. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kåreholt I, Winblad B, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol. 2005;62(10):1556-60. Disponible en: https://doi.org/10.1001/archneur.62.10.1556

672. Qiu C, Winblad B, Viitanen M, Fratiglioni L. Pulse pressure and risk of Alzheimer disease in persons aged 75 years and older: a community-based, longitudinal study. Stroke. 2003;34(3):594-9. Disponible en: https://doi.org/10.1161/01.STR.0000060127.96986.F4

673. Penagos SP, Salazar LD, Vera FE. Control de signos vitales. Guías para manejo de Urgencias. Bogotá (Colombia): Fundación Cardioinfantil. 2005; 9:1465-1473. Disponible en: http://hectorfutbool.mex.tl/images/32235/Control_de_signos_vitales.pdf

674. Borba de Amorim R, Coelho Santa Cruz MA, Borges de Souza-Júnior PR, Corrêa da Mota J, González H C. Medidas de estimación de la estatura aplicadas al índice de masa corporal (IMC) en la evaluación del estado nutricional de adultos mayores. Rev Chil Nutr. noviembre de 2008; 35:272-9. Disponible en: https://doi.org/10.4067/S0717-75182008000400003

675. Abreu Viamontes C, Burgos Bencomo Y de los D, Cañizares Inojosa D, Viamontes Cardoso A. Estado nutricional en adultos mayores. Rev Arch Méd Camagüey. octubre de 2008;12(5):0-0. Disponible en: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1025-02552008000500005

676. Aranceta-Bartrina J, Serra-Majem L, Foz-Sala M, Moreno-Esteban B. Prevalencia de obesidad en España. Med Clin. 2005; 125 (12): 460-466. Disponible en: https://doi.org/10.1157/13079612

677. Ce N, Bj H. Glucemia de ayuno en un grupo de pacientes diabéticos de Jalisco, México. Archivos en medicina familiar. 2005; 7 (1): 10-13. Disponible en: https://www.redalyc.org/pdf/507/50770104.pdf

678. Gutiérrez-Abejón E, Rejas-Gutiérrez J, Criado-Espegel P, Campo-Ortega EP, Breñas-Villalón MT, Martín-Sobrino N. Impacto del consumo de tabaco sobre la mortalidad en España en el año 2012. Med Clínica. 21 de diciembre de 2015;145(12):520-5. Disponible en: https://doi.org/10.1016/j.medcli.2015.03.013

679. García-Díaz V, Fernández-Feito A, Arias L, Lana A. Consumo de tabaco y alcohol según la jornada laboral en España. Gac Sanit. septiembre de 2015; 29(5):364-9. Disponible en: https://doi.org/10.1016/j.gaceta.2015.04.014

680. Zaragoza Martí A. Adherencia a la dieta mediterránea y su relación con el estado. Nutr Hosp. 1 de abril de 2015;(4):1667-74. Disponible en: https://dx.doi.org/10.3305/nh.2015.31.4.8553

681. BOE.es - Documento BOE-A-2003-20257 [Internet]. [citado 24 de febrero de 2019]. Disponible en: https://www.boe.es/diario_boe/txt.php?id=BOE-A-2003-20257

682. Reed GM, Anaya C, Evans SC. ¿Qué es la CIE y por qué es importante en la psicología? Int J Clin Health Psychol. 2012; 13 (3): 461-473. [Internet]. 2012 [citado 24 de febrero de 2019];12(3). Disponible en: http://www.redalyc.org/resumen.oa?id=33723713007

683. Osornio L, Montenegro S, Marti G, Toselli L, Otero C, Tavasci I, et al. Codificación múltiple de una lista de problemas utilizando la CIAP-2, CIE-10 y SNOMED CT. Inf 2004; Disponible en: https://www.researchgate.net/profile/Sergio-Montenegro-2/publication/266040780_Codificacion_multiple_de_una_lista_de_problemas_utilizando_la_CIAP-2_CIE-10_y_SNOMED_CT/links/5427d1e90cf26120b7b373f0/Codificacion-multiple-de-una-lista-de-problemas-utilizando-la-CIAP-2-CIE-10-y-SNOMED-CT.pdf

ANEXOS/APPENDIXES

ANEXOS/APPENDIXES

"La memoria puede dormir y no recordar, pero el corazón nunca olvidará lo que ha sentido.".

(Sam)

ANEXO 1/APPENDIX 1

Tabla A 1. Characteristics of studies included in the meta-analysis

			Cases			Controls		
Study (*N* = 100)	**Year**	**Country**	***n***	**% F**	**Age**	***n***	**% F**	**Age**
Zhou et al. (563)								
1. Ban et al. (564) *	2009	Japan	197	59.90	80 ± 1	47	38.30	75 ± 1
2. Cacabelos et al. (565)	2003	Spain	147	-	71.73 ± 9.61	109	-	50.20 ± 12.06
3. Caramelli et al.(566)	1999	Brazil	24	-	67.2 ± 10.6	32	59.38	68.2 ± 10.6
4. Chen et al. (567)	2019	China	117	52.14	67.64 ± 6.65	117	62.39	66.06 ± 6.00
5. Hoshino, Kamino, Matsumoto (568) *	2002	Japan	82	71.95	77.0 ± 6.8	40	67.50	84.2 ± 3.1
6. Kouzuki et al. (569)	2018	Japan	42	61.90	80.5 ± 5.7	18	72.22	75.6 ± 5.5
7. Kuo et al. (570) *	1998	America	64	-	81.6 ± 0.9	36	-	78.7 ± 1.3
8. Lehtonen, Luutonen (571)	1986	Finland	22	100.00	≥90	23	100.00	≥90
9. Lesser et al. (572)	2001	America	44	-	87.0 ± 8.5	22	-	82.0 ± 7
10. Macesic et al. (573)	2017	Serbia	62	70.97	73.1 ± 5.8	40	50.00	68.4 ± 5.5
11. Mamo et al. (574)	2008	Australia	10	-	79.2 ± 1.8	10	-	80.5 ± 1.5
12. Moroney et al. (575)	1999	America	225	72.00	77.7 ± 6.3	764	67.54	74.1 ± 5.5
13. Panza et al. (576)	2003	Italy	49	69.39	71.6 ± 9.3	45	71.11	65.8 ± 11.6
14. Paragh et al. (577)	2002	Hungary	30	66.67	64.3 ± 11.7	40	65.00	72.3 ± 9.6
15. Reitz et al. (578)	2004	America	244	77.46	82.85 ± 7.3	2226	65.86	76.42 ± 6.3
16. Ryglewicz et al. (579)	2002	Poland	26	-	67 ± 8.4	46	-	67.5 ± 6.9
17. Scacchi et al. (580)	1998	Italy	80	71.25	83.5 ± 5.9	155	76.77	78.3 ± 7.0
18. Shafagoj et al. (581)	2018	Jordan	38	63.16	74.2 ± 5.4	33	66.67	72.4 ± 6.3

			Cases			Controls		
Study (*N* = 100)	**Year**	**Country**	***n***	**% F**	**Age**	***n***	**% F**	**Age**
19. Solfrizzi et al. (582) *	2002	Italy	49	75.51	71.6 ± 9.3	45	71.11	65.8 ± 11.6
20. Tang et al. (583)	2019	China	143	45.45	62.89 ± 8.38	140	46.43	64.10 ± 9.49
21. Warren, Hynan, Weiner (584)	2012	America	150	70.00	79.5 ± 6.17	197	69.04	70 ± 6.33
22. Watanabe et al. (585) *	2005	Japan	106	-	79 ± 7	227	-	76 ± 10
23. Werh et al. (586)	2006	Sweden	97	90.72	77.9 ± 3.0	139	94.24	78.5 ± 3.0
24. Wolf et al. (587)	2004	Japan	25	4.00	80 ± 6	26	34.62	77 ± 5
25. Yamamoto et al. (588)	2005	Turkey	61	19.67	74.1 ± 7.4	32	38.46	74.5 ± 6.3
26. Yavuz et al. (589)	2008	Poland	132	75.00	71.8 ± 7.9	158	58.86	70.5 ± 8.8
Liu et al. (590)								
Lehtonen, Luutonen (571)*	1986	Finland	22	-	>90	23	-	>90
Kuo et al. (570)	1998	USA	64	-	81.6	36	-	78.7
27. Kalman et al. (591)	1999	USA	24	75.00	70.2	15	73.00	64.8
28. Merched et al. (592)	2000	France	98	71.4	77.56	59	52.5	75.37
Solfrizzi et al. (582)	2002	Italy	18	0.00	74.2	30	0.00	68.4
Solfrizzi et al. (582)	2002	Italy	43	100.00	70.2	33	100.00	67
29. Lesser et al. (593)[1]	2009	USA	144	-	-	151	-	-
30. Sun et al. (594)	2010	China	45	64.00	59-92	44	68.00	58-87
31. Preseki et al. (595)	2011	Croatia	50	-	79.1	58	-	71.6
32. Parnowski, Kaluza # (596)	2013	Poland	39	66.6	80.12	44	75.00	72.95
33. R V ~	2016	India	167	0.00	69.8	984	0.00	63.1
R V ~	2016	India	137	100.00	67.8	882	100.00	62.4
34. Grossi et al. (597)	2018	Brazi	40	30.00	78(7)	40	31.00	76.5

			Cases			Controls		
Study (*N* = 100)	**Year**	**Country**	***n***	**% F**	**Age**	***n***	**% F**	**Age**
Wu et al. (598)								
35. Agarwal et al. (599)	2015	Indian	39	69	67±9	42	52	62±8
36. Alam et al. (600)	2014	Indian	75	68	66±9	120	63	63±8
Ban et al. (564)	2009	Japanese	197	40	80±1	47	62	75±1
37. Cankurtaran et al. (601)	2005	Turks	120	34	74±8	803	37	71±6
38. Chang et al. (602)	2014	Chinese	44	/	80±9	62	NA	80±8
39. Duan, Ling, Zhou (603)	2006	Chinese	62	47	65±3	50	60	56±3
40. Han (604)	2005	Chinese	27	33	72±11	27	NA	NA
Hoshino, Kamino, Matsumoto (568)	2002	Japanese	82	28	84±3	40	33	/77±7
41. Li (605)	2014	Chinese	45	36	64±2	45	36	64±3
42. Liu, Chen (606)	2006	Chinese	31	45	69±7	40	43	69±8
43. Liu (607)	2005	Chinese	268	47	74±3	325	46	74±2
44. Raygani et al. (608)	2006	Iranians	94	44	74±10	111	37	72±11
45. Shim (609)	2010	Korean	78	40	72±9	58	36	63±7
46. Singh et al. (610)	2012	Indian	70	76	NA	75	NA	NA
47. Sun (611)	2006	Chinese	82	55	81±3	46	83	78±4
48. Vasantharekha et al. (612)	2016	Indian	304	47	69±5	1868	53	63±2
49. Wada (613)	2000	Japanese	36	29	77±5	15	13	72±6
50. Wang (614)	2005	Chinese	35	35	69±8	16	44	70±7
51. Wang (615)	2006	Chinese	124	47	NA	80	50	NA
52. Wang (616)	2017	Chinese	43	44	67±10	45	36	64±6
53. Wang (617)	2016	Chinese	39	41	68±7	40	45	71±7

			Cases			Controls		
Study (*N* = 100)	**Year**	**Country**	***n***	**% F**	**Age**	***n***	**% F**	**Age**
Wang (617)	2016	Chinese	34	/	74±8	40	45	71±7
54. Watanabe et al. (618)	2004	Japanese	34	76	76±9	63	NA	72±11
Watanabe et al. (585)	2005	Japanese	106	55	79±7	227	70	76±10
55. Xiao et al. (619)	2012	Chinese	104	36	78±7	104	54	77±6
56. Xiaohong et al. (620)	2010	Chinese	45	39	59 ~ 92	44	32	58 ~ 87
Yamamoto et al. (588)	2005	Japanese	61	33	80±6	32	53	77±5
57. Yang, Tian, Zhong (621)	2007	Chinese	15	45	73±8	29	56	60±7
58. Yu et al. (622)	2014	Chinese	201	33	77±6	257	47	76±7
59. Yuan et al. (623)	2006	Chinese	30	38	71±7	60	30	65±6
60. Yue (624)	2009	Chinese	111	48	69±9	117	38	66±9
61. Zengi et al. (625)	2012	Turks	21	50	76±8	20	55	81±7
62. Zhao et al. (626)	2014	Chinese	48	33	69±6	37	51	71±6
63. Zheng et al. (627)	2016	Chinese	207	50	81±8	256	35	82±6
64. Zhong et al. (628)	2016	Chinese	54	55	70±8	54	54	71±7
65. Zhou (629)	2015	Chinese	40	45	68±2	40	58	68±3
66. Zhu (630)	2007	Chinese	31	43	69±7	40	43	69±7
Wang et al. (631)								
67. Papassotiropoulos et al. (632)	2002		32	62.00	69 ± 8	7	29.00	55 ± 10
68. Martínez-Morillo et al. (633)	2014		38	64.00	(60-94)	37	53.00	(43-80)
69. Kölsch et al. (634)	2006		75	63.40	68.4 ± 7.9	39	53.80	65.9 ± 11.4
70. Kölsch et al. a (635)	2009		118	61.90	68.5 ± 7.9	62	57.90	70.4 ± 7.1
71. Kölsch et al. b (636)	2009		149	69.10	74.1 ± 7.9	86	53.50	72.8 ± 7.6

			Cases			Controls		
Study (*N* = 100)	**Year**	**Country**	***n***	**% F**	**Age**	***n***	**% F**	**Age**
72. Kölsch et al. (637)	2010		90	63.90	70.6 ± 8.3	57	51.60	69.3 ± 6.8
73. Qureischie et al. (638)	2008		104	68.00	72.5 ± 8.8	49	72.40	72.4 ± 7.9
74. Mateos et al. (639)	2011		21	66.70	67.3 ± 1.70	28	67.90	57.8 ± 1.27
75. Wollmer et al. (640)	2003		24	58.00	73.5 ± 5.5	22	49.40	70.1 ± 6.3
76. Wollmer et al. (641)	2003		24	-	71.7 ± 7.8	22	-	65.6
77. Shafaati et al. (642)	2007		17	41.20	(62–83)	43	65.10	(18–85)
78. Schönknecht et al. (643)	2002		17	42.90	75.4 ± 10.3	55	40.00	69.0 ± 5.8
79. Popp et al. (644)	2012		53	62.30	71.23 ± 8.29	43	51.20	67.33 ± 9.04
80. Popp et al. (645)	2013		106	64.20	71.1 ± 7.87	87	49.40	67.7 ± 9.13
81. Vanmierlo et al. (646)	2011		67	44.80	71.8 ± 7.5	29	62.70	69.0 ± 6.9
82. Leoni, Caccia (647)	2013		24	70.80	66.8 ± 8.0	28	65.80	68.6 ± 2.85
Xu et al. (648)								
83. Tan et al. (649)	2003	USA	77	-	-	1026	62.96	76.1
84. Li et al. (650)	2005	USA	152	-	-	2123	59.20	74.9
85. Solomon et al. (651)	2009	USA	469	59.91	69.90	9844	0	-
86. Mielke et al. (652)	2010	Sweden	46	-	-	648	0	-
87. Huang et al. (653)	20s14	Taiwan	612	-	-	142744	48.20	-
88. Kivipelto et al. (654)	2005	Karelia	48	-	-	1449	63.14	-
89. Reitz et al. (655)	2010	USA	101	65.34	79.70	1130	65.66	75.7
90. Kimm et al. (656)	2011	Korea	821	-	-	490445	0	51.9

				Cases			Controls	
Study (*N* = 100)	**Year**	**Country**	***n***	**% F**	**Age**	***n***	**% F**	**Age**
Kimm et al. (656)	2011	Korea	1030	100	-	358060	100	53.6
91. Kivipelto et al. (657)	2002	Finland	48	-	-	1449	66.04	-
92. Hayden et al. (658)	2006	UK	104	73.07	81.50	3264	58.24	74
93. Notkola et al. (659)	1998	Finland	27	-	-	444	0	-
94. Rönnemaa et al. (660)	2012	Sweden	127	-	-	2268	-	49.6
95. Wang et al. (661)	2012	Taiwan	8488	-	-	1230400	51.95	-
96. Lieb et al. (662)	2012	USA	18	100	73.97	99	100	-
97. Dal Forno et al. (663)	2005	USA	40	-	-	576	0	66.8
Dal Forno et al. (663)	2005	USA	67	100	-	781	100	64
Singh et al. (610)	2012	India	0	-	-	0	-	-
98. Forti et al. (664)	2010	Italy	18	-	-	466	51.28	69.3
Forti et al. (664)	2010	Italy	30	-	-	238	67.64	79.8
99. Raffaitin et al. (665)	2009	France	134	-	-	7087	60.99	-
100.Muller et al. (666)	2007	USA	147	-	-	1833	67.32	76.1
Singh et al. (610)	2012	India	0	-	-	145	-	-

*K=6 articles were duplicated in LDL-C. The number of participants were deleted for main analysis.

[1] Total N Cases = 144; n/LDL-C=41; n/HDL-C=41; n/TC=62; Total N Control = 151; n/LDL-C=48; n/HDL-C=48; n/TC=55

Tabla A 2. Factors included in primary meta-analysis that showed positive and negative association with AD.

Study	LDL_C		TC		HDL_C		TG	
	***SMD IC* (95%)**	**Weight**						
Ban Y (564)	0.80 (0.47 ~ 1.12)	4.1	-	-	-	-	-	-
Cacabelos R (565)	0.01 (-0.24 ~ 0.26	4.2	-	-	-	-	-	-
Caramelli P (566)	0.14 (-0.39 ~ 0.67)	3.6	-	-	-	-	-	-
Chen H (567)	1.19 (0.91 ~ 1.47)	4.2	-	-	-	-	-	-
Hoshino T (568)	0.34 (-0.04 ~ 0.72)	3.9	-	-	-	-	-	-
Kouzuki M (569)	-0.22 (-0.77 ~ 0.34)	3.5	-	-	-	-	-	-
Kuo YM (570)	4.45 (3.70 ~ 5.20)	3.0	-	-	-	-	-	-
Lehtonen A (571)	0.57 (-0.03 ~ 1.17)	3.4	-	-	-	-	-	-
Lesser G (572)	0.32 (-0.19 ~ 0.84)	3.6	-	-	-	-	-	-
Macesic M (573)	1.07 (0.65 ~ 1.50)	3.8	-	-	-	-	-	-
Mamo JC (574)	-0.16 (-1.04 ~ 0.72)	2.7	-	-	-	-	-	-
Moroney JT (575)	-0.25 (-0.40 ~ -0.10)	4.3	-	-	-	-	-	-
Panza F (576)	-0.63 (-1.04 ~ -0.21)	3.9	-	-	-	-	-	-
Paragh G (577)	2.04 (1.46 ~ 2.63)	3.4	-	-	-	-	-	-
Reitz C (578)	-0.00 (-0.13 ~ 0.13)	4.4	-	-	-	-	-	-
Ryglewicz D (579)	0.29 (-0.20 ~ 0.77)	3.7	-	-	-	-	-	-
Scacchi R (580)	-0.45 (-0.73 ~ -0.18)	4.2	-	-	-	-	-	-
Shafagoj YA (581)	-0.32 (-0.79 ~ 0.15)	3.7	-	-	-	-	-	-
Solfrizzi V (582)	-0.69 (-1.11 ~ -0.28)	3.9	-	-	-	-	-	-
Tang Y (583)	0.39 (0.15 ~ 0.62)	4.2	-	-	-	-	-	-
Warren MW (584)	0.50 (0.28 ~ 0. 72)	4.3	-	-	-	-	-	-

Study	LDL_C		TC		HDL_C		TG	
Watanabe T (585)	0.17 (-0.06 ~ 0.40)	4.2	-	-	-	-	-	-
Werh H (586)	0.36 (0.10 ~ 0.62)	4.2	-	-	-	-	-	-
Wolf H (587)	0.20 (-0.35 ~ 0.75)	3.50	-	-	-	-	-	-
Yamamoto H (588)	0.08 (-0.35 ~ 0.51)	3.80	-	-	-	-	-	-
Yavuz BB (589)	-0.02 (-0.25 ~ -0.21)	4.20	-	-	-	-	-	-
	***OR IC* (95%)**	**Weight**	***SMD IC* (95%)**	**Weight**	***SMD IC* (95%)**	**Weight**	***SMD IC* (95%)**	**Weight**
Lehtomen (667)	0.58 (-0.02 ~ 1.18)	10.86	0.43 (-0.16 ~ 1.02)	7.53	-0.02 (-0.61-0.56)	8.77	0.19 (-0.40 ~ 0.77)	6.32
Kuo YM (570)	4.49 (3.74 ~ 5.24)	10.36	0.00 (-0.65 ~ 0.65)	7.54	-2.76 (-3.33 ~ -2.20)	8.82		-
Kalman J (591)	-0.19 (-0.83 ~ 0.46)	10.71	-0.40 (-0.72 ~ -0.07)	7.44	0.75 (0.08 ~ 1.42)	8.54	-0.31 (-0.96 ~ 0.34)	5.77
Merched A (592)	-	-	-1.15 (-1.78 ~ -0.52)	7.89	-1 (-1.34 ~ -0.66)	1.29	-0.26 (-0.5 ~ 0.07)	8.95
Solfrizzi V (582)	-	-	-0.17 (-0.62 ~ 0.28)	7.46	-	-	-	-
Solfrizzi V (582)	-	-	4.83 (4.11 ~ 5.55)	7.73	-	-	-	-
Lesser GT (593)	3.26 (2.62 ~ 3.90)	10.73	0.57 (0.15 ~ 1)	7.29	1.38 (0.92-1.85)	9.05	-	-
Sun X (594)	-	-	0.45 (0.07 ~ 0.84)	7.77	-0.29 (-0.71 ~ 0.13)	9.15	-	-
Preseki P (595)	0.43 (0.05 ~ 0.81)	11.39	-0.31 (-0.74 ~ 0.13)	7.82	0.48 (80.10 ~ 0.87)	9.21	0.54 (0.15 ~ 0.92)	8.32
Parnowski T # (596)	0.45 (0.01 ~ 0.89)	11.27	1.23 (1.05 ~ 1.40)	7.76	-1.04 (-1.50 ~ -0.58)	9.06	0.06 (-0.50 ~ 0.62)	6.57
R V	1.30 (1.12 ~ 1.47)	11.71	1.87 (1.67 ~ 2.07)	8.01	-1.50 (-1.67 ~ -1.32)	9.51	-	-
R V	2.26 (2.05 ~ 2.46)	11.68	-0.28 (-0.72 ~ 0.16)	7.99	-1.51 (-1.70 ~ -1.32)	9.49	-	-
Grossi MF (597)	0.25 (-0.19-0.69)	11.27	0.76 (0.13 ~ 1.40)	7.75	-0.16 (-0.60 ~ 0.28)	9.11	-0.75(-1.20 ~ -0.30)	7.61
	***OR IC* (95%)**		***OR IC* (95%)**					-
Agarwal R (599)	0.13 (-0.31 ~ 0.56)	-	0.28 (-0.16 ~ 0.72)	-	0.13 (-0.31 ~ 0.56)	-	0.18 (-0.11 ~ 0.46)	-
Alam R (600)	0.15 (-0.14 ~ 0.44)	-	0.12 (-0.17 ~ 0.41)	-	-0.22 (-0.51 ~ 0.07)	-	-	-
Ban Y (564)	0.80 (0.47 ~ 1.12)	-	-	-	1.26 (0.92 ~ 1.60)	-	-1.24 (-1.58 ~ -0.91)	-

Study	LDL_C		TC		HDL_C		TG	
Cankurtaran M (601)	-0.02 (-0.21 ~ 0.17)	-	0.04 (-0.15 ~ 0.23)	-	0.08 (-0.11 ~ 0.27)	-	0.03 (-0.16 ~ 0.22)	-
Chang L (602)	-	-	0.15 (-0.23 ~ 0.54)	-	0.11 (-0.27 ~ 0.50)	-	-0.08 (-0.46 ~ 0.31)	-
Duan D (603)	-	-	0.82 (0.43 ~ 1.21)	-	-	-	0.78 (0.40 ~ 1.17)	-
Han JF (604)	0.00 (-0.53 ~ 0.53)	-	0.00 (-0.53 ~ 0.53)	-	0.00 (-0.53 ~ 0.53)	-	0.00 (-0.53 ~ 0.53)	-
Hoshino T (568)	0.34 (-0.04 ~ 0.72)	-		-	-0.08 (-0.46 ~ 0.30)	-	-	-
Li W (605)	-0.01 (-0.42 ~ 0.40)	-	0.00 (-0.41 ~ 0.41)	-	-0.07 (-0.48 ~ 0.34)	-	-	-
Liu JH (606)	0.85 (0.36 ~ 0.69)	-	0.79 (0.30 ~ 1.28)	-	0.05 (-0.42 ~ 0.52)	-	0.91 (0.42 ~ 1.40)	-
Liu ZS (607)	0.52 (0.36 ~ 1.34)	-	0.33 (0.16 ~ 0.49)	-	-0.09 (-0.25 ~ 0.08)	-	0.06 (-0.10 ~ 0.23)	-
Raygani AV (608)	0.52 (0.24 ~ 0.80)	-	0.38 (0.10 ~ 0.65)	-	-0.74 (-1.02 ~ -0.45)	-	0.17 (-0.11 ~ 0.44)	-
Shim YS (609)	-0.29 (-0.64 ~ 0.05)	-	-0.28 (-0.62 ~ 0.06)	-	0.16 (-0.18 ~ 0.50)	-	-	-
Singh NK (610)	0.95 (0.61 ~ 1.30)	-	1.38 (1.02 ~ 1.74)	-	-0.54 (-0.87 ~ -0.21)	-	0.00 (-0.33 ~ 0.32)	-
Sun YL (611)	-0.29 (-0.65 ~ 0.07)	-	-0.11 (-0.47 ~ 0.26)	-	0.03 (-0.33 ~ 0.39)	-	0.14 (-0.22 ~ 0.50)	-
Vasantharekha R (612)	1.72 (1.59 ~ 1.85)	-	1.50 (1.37 ~ 1.63)	-	-1.48 (-1.61 ~ -1.36)	-	0.17 (0.05 ~ 0.29)	-
Wada H (613)	-0.14 (-0.74 ~ 0.47)	-	-0.37 (-0.98 ~ 0.24)	-	0.24 (-0.36 ~ 0.85)	-	-0.58 (-1.19 ~ 0.04)	-
Wang CY (614)	0.54 (-0.06 ~ 1.14)	-	0.61 (0.01 ~ 1.22)	-	0.14 (-0.45 ~ 0.73)	-	0.82 (0.21 ~ 1.43)	-
Wang H (615)	1.62 (1.29 ~ 1.94)	-	-0.20 (-0.49 ~ 0.08)	-	-0.23 (-0.51 ~ 0.06)	-	1.36 (1.05 ~ 1.67)	-
Wang R (616)	-	-	-	-	-0.94 (-1.38 ~ -0.50)	-	-	-
Wang XH a (617)	0.00 (-0.44 ~ 0.44)	-	0.00 (-0.44 ~ 0.44)	-	0.00 (-0.44 ~ 0.44)	-	-	-
Wang XH b (617)	0.25 (-0.21 ~ 0.71)	-	0.15 (-0.31 ~ 0.61)	-	0.00 (-0.46 ~ 0.46)	-	-	-
Watanabe T (618)	0.03 (-0.39 ~ 0.45)	-	-0.27 (-0.69 ~ 0.15)	-	0.00 (-0.42 ~ 0.42)	-	-0.34 (-0.75 ~ 0.08)	-
Watanabe T (585)	0.17 (-0.06 ~ 0.40)	-	-0.08 (-0.31 ~ 0.16)	-	0.32 (0.09 ~ 0.55)	-	-0.27 (-0.50 ~ -0.04)	-
Xiao Z (619)	0.08 (-0.19 ~ 0.35)	-	0.39 (0.12 ~ 0.67)	-	-0.35 (-0.63 ~ 0.08)	-	0.06 (-0.21 ~ 0.33)	-
Xiaohong W (620)	-	-	0.57 (0.15 ~ 1.00)	-	-0.73 (-1.16 ~ -0.30)	-	-	-

Study	LDL_C		TC		HDL_C		TG	
Yamamoto H (588)	0.08 (-0.35 ~ 0.51)	-	-0.07 (-0.50 ~ 0.35)	-	0.06 (-0.37 ~ 0.49)	-	-0.22 (-0.64 ~ 0.21)	-
Yang CZ (621)	-0.40 (-1.03 ~ 0.23)	-	-0.08 (-0.71 ~ 0.54)	-	0.55 (-0.09 ~ 1.18)	-	-0.19 (-0.81 ~ 0.44)	-
Yu ZL (622)	0.13 (-0.06 ~ 0.31)	-	0.30 (0.12 ~ 0.49)	-	-0.02 (-0.20 ~ 0.17)	-	-0.10 (-0.29 ~ 0.08)	-
Yuan YG (623)	-1.06 (-1.53 ~ -0.60)	-	0.81 (0.35 ~ 1.26)	-	-0.06 (-0.50 ~ 0.38)	-	0.66 (0.22 ~ 1.11)	-
Yue YH (624)	0.14 (-0.12 ~ 0.40)	-	0.31 (0.05 ~ 0.57)	-	-0.11 (-0.37 ~ 0.15)	-	0.46 (0.19 ~ 0.72)	-
Zengi Q (625)	-0.57 (-1.19 ~ 0.06)	-	-0.87 (-1.51 ~ -0.23)	-	-0.26 (-0.88 ~ 0.35)	-	-1.48 (-2.17 ~ -0.79)	-
Zhao Z (626)	0.05 (-0.38 ~ 0.48)	-	-0.26 (-0.69 ~ 0.18)	-	-0.96 (-1.42 ~ -0.51)	-	0.85 (0.40 ~ 1.30)	-
Zheng JQ (627)	0.08 (-0.10 ~ 0.27)	-	0.16 (-0.02 ~ 0.35)	-	-0.21 (-0.39 ~ -0.03)	-	0.33 (0.15 ~ 0.52)	-
Zhong X (628)	0.58 (0.19 ~ 1.30)	-		-		-	0.79 (0.40 ~ 1.18)	-
Zhou TT (629)	0.84 (0.39 ~ 1.30)	-	0.78 (0.32 ~ 1.23)	-	0.10 (-0.34 ~ 0.54)	-	-	-
Zhu JY (630)	0.85 (0.36 ~ 1.34)	-	0.79 (0.30 ~ 1.28)	-	0.05 (-0.42 ~ 0.52)	-	0.91 (0.42 ~ 1.40)	-
			***SMD IC* (95%)**					-
Papassotiropoulos A (632)	-	-	0.68 (-0.15 ~ 1.52)	-	-	-	-	-
Martínez-Morillo E (633)	-	-	0.06 (-0.40 ~ 0.51)	-	-	-	-	-
Kölsch H (634)	-	-	-2.78 (-3.31 ~ -2.25)	-	-	-	-	-
Kölsch H (635)	-	-	-0.91 (-1.23 ~ -0.58)	-	-	-	-	-
Kölsch H (636)	-	-	-0.62 (-0.89 ~ -0.35)	-	-	-	-	-
Kölsch H (637)	-	-	-0.45 (-0.78 ~ -0.11)	-	-	-	-	-
Qureischie H (638)	-	-	-1.28 (-1.65 ~ -0.91)	-	-	-	-	-
Mateos L (639)	-	-	0.40 (-0.17 ~ 0.97)	-	-	-	-	-
Wollmer MA (640)	-	-	-0.72 (-1.31 ~ -0.12)	-	-	-	-	-
Wollmer MA (641)	-	-	-0.67 (-1.26 ~ -0.07)	-	-	-	-	-
Shafaati M (642)	-	-	2.68 (1.93 ~ 3.43)	-	-	-	-	-

Study	LDL_C		TC		HDL_C		TG	
Schönknecht P (643)	-	-	0.44 (-0.11 ~ 0.99)	-	-	-	-	-
Popp J (644)	-	-	-0.37 (-0.77 ~ 0.04)	-	-	-	-	-
Popp J (645)	-	-	-0.42 (-0.71 ~ -0.13)	-	-	-	-	-
Vanmierlo T (646)	-	-	-0.30 (-0.74 ~ 0.14)	-	-	-	-	-
Leoni (668)	-	-	1.10 (0.52 ~ 1.69)	-	-	-	-	-
			***RR IC* (95%)**	**Weight**	***RR IC* (95%)**	**Weight**		-
Tan ZS (649)	-	-	0.97 (0.90 ~ 1.05)	16.01	-	-	-	-
Li G (650)	-	-	1.00 (0.61 ~ 1.62)	5.4	1.23 (0.71 ~ 2.15)	3.68	-	-
Solomon A (651)	-	-	1.58 (1.22 ~ 2.06)	6.83	-	-	-	-
Mielke MM (652)	-	-	2.82 (0.94 ~ 8.43)	0.14	-	-	-	-
Huang C-C (653)	-	-	1.06 (0.75 ~ 1.51)	7.65	-	-	-	-
Kivipelto M (654)	-	-	2.12 (1.05 ~ 4.30)	0.74	-	-	-	-
Reitz C (655)	-	-	0.80 (0.40 ~ 1.50)	4.79	-	-	-	-
Kimm H (656)	-	-	1.20 (1.00 ~ 1.50)	11.06	-	-	-	-
Kimm H (656)	-	-	1.10 (0.90 ~ 1.30)	12.6	-	-	-	-
Kivipelto M (657)	-	-	2.80 (1.20 ~ 6.70)	0.26	-	-	-	-
Hayden KM (658)	-	-	0.47 (0.19 ~ 0.98)	7.33	-	-	-	-
Notkola IL (659)	-	-	3.10 (1.20 ~ 8.50)	0.15	-	-	-	-
Ronnemaa E (660)	-	-	1.00 (0.90 ~ 1.20)	14.13	-	-	-	-
Wang K-C (661)	-	-	0.69 (0.66 ~ 1.32)	10.80	-	-	-	-
Lieb W (662)	-	-	0.80 (0.20 ~ 2.50)	1.41	1.60 (0.50 ~ 5.50)	0.3	-	-
Dal Forno G (663)	-	-	0.59 (0.23 ~ 1.53)	3.74	-	-	-	-
Dal Forno G (663)	-	-	0.35 (0.14 ~ 0.89)	7.76	-	-	-	-

Study	LDL_C		TC		HDL_C		TG	
Singh NK (610)	-	-	1.15 (1.01 ~ 1.32)	15.70	-	-	-	-
Forti P (664)	-	-	-	-	0.56 (0.12 ~ 2.71)	1.14	-	-
Forti P (664)	-	-	-	-	0.83 (0.27 ~ 2.49)	1.55	-	-
Raffaitin C (665)	-	-	-	-	0.80 (0.27 ~ 2.49)	6.91	-	-
Muller M (666)	-	-	-	-	1.00 (0.70 ~ 1.40)	15.56	-	-
Singh NK (610)	-	-	1.15 (1.01 ~ 1.32)	9.79	1.02 (0.86 ~ 1.19)	1	-	-

ANEXO 2/APPENDIX 2

Tabla A 3. Characteristics of studies included in the meta-analysis

	Year[1]	**Country[2]**	**Age[3]**	**Women[4]**	**n AD[5]**	**SBP[6]**	**DBP[7]**	**SBP and DBP[8]**
Gabin et al.(669)	2017	Norway	61,8	53	383	1,11 (1,00 - 1,23)	*	*
McGrath et al.(230)	2017	USA	55	53	81	1,11 (0,97 - 1,27)	*	*
Chiang et al.(231)	2007	Taiwan	57,9	41	64	1,26 (0,64-2,49)	*	*
Kivipelto et al. (120)	2001	Finland	50,4	61	48	2,80 (1,09-7,15)	*	*
Morris et al. (212)	2001	USA	63	63	41	1,03 (0,80-1,32)	1.56 (0.6-4.07)	*
Kimm et al. (232)	2011	Korea	52,6	0	821	1,40 (1,09-1,79)	*	*
Ninomiya et al. (233)	2011	Japan	57,4	60	1153	0,84 (0,42-1,67)	*	*
Qiu et al. a(265)	2010	Suecia	81.5±5	75	150	1.84 (1.06-3.18)	0.78 (0.54-1.12)	*
	*	*	*	*	124	1.47 (1.02-2.12)	*	*
Li et al. (266)	2007	USA	65-74	59	14	1.38 (0.71-2.70)	0.82 (0.29-2.35)	*
	*	*	*	*	19	1.47 (0.80-2.71)	*	*
Li et al. (266)	2007	USA	75-84	59	37	0.94 (0.62-1.42)	0.73 (0.34-1.59)	*
	*	*	*	*	31	0.60 (0.38-0.92)	*	*
Launer et al.(62)	2000	USA	*	0	87	1,22 (0,37-4,04)	1,86 (1,01-3,46)	*
Verghese et al.(234)	2003	USA	*	32	65	0,68 (0,35-1,32)	1,91 (1,05-3,48)	*
Posner et al.(211)	2002	USA	*	55	257	0,80 (0,42-1,60)	*	*
Bermejo et al.(235)	2010	Spain	*	28	113	2,07 (0,98-4,37)	*	*

	Year[1]	Country[2]	Age[3]	Women[4]	n AD[5]	SBP[6]	DBP[7]	SBP and DBP[8]
Huang et al.(236)	2014	China-Taiwan	*	24	612	1,3 (1,07-1,59)	*	*
Chu et al.(237)	2010	China-Hongkong	75,1	0	10	1,044 (1,00-1,07)	*	*
Luchsinger et al.(166)	2005	USA	76,2	35	246	1,4 (0,9-2,1)	*	*
Forti et al.(238)	2010	Italy	69,3	26	18	0,77 (0,17-3,52)	*	*
Forti et al.(238)	2010	Italy	79,8	34	30	0,97 (0,39-2,4)	*	*
Song et al.(239)	2011	Canada	*	*	416	1 (0,75-1,32)	*	*
Raffaitin et al.(240)	2009	Franca	*	30	134	1,1 (0,6-2,01)	*	*
Muller et al.(241)	2007	USA	76,1	34	147	1,5 (0,9-2,4)	*	*
Lindsay et al.(242)	2002	Canada	*	63	194	0,88 (0,62-1,27)	*	*
Tyas et al.(170)	2001	Canada	*	*	35	1,14 (0,53-2,45)	*	*
Kimm et al.(232)	2011	Korea	53,6	100	1030	1,2 (0,38-4,04)	*	*
Kivipelto et al.(243)	2002	Finland	*	33	48	2,6 (1,1-6,6)	*	*
Borenstein et al.(77)	2005	Japan	*	*	90	1,79 (0,82-3,89)	*	*
Hayden et al.(244)	2006	UK	77,75	66	104	0,66 (0,43-1,02)	*	*
Kuller et al.(245)	2003	USA	*	*	330	0,9 (0,57-1,48)	*	*
Ronnemaa et al.(246)	2011	Sweden	49,6	*	127	1 (0,99-1,01)	*	*
Annweiler et al.(247)	2012	France	79,84	*	70	0,7 (0,38-1,29)	*	*

	Year[1]	**Country[2]**	**Age[3]**	**Women[4]**	**n AD[5]**	**SBP[6]**	**DBP[7]**	**SBP and DBP[8]**
Wang et al.(248)	2012	China-Taiwan	*	26	8488	1,38 (1,07-1,75)	*	*
Qiu et al. (249)	2006	Sweden	*	37	333	1,32 (0,97-1,81)	1,9 (1,36-2,68)	*
Olazaran et al.(250)	2013	Spain	*	*	68	0,64 (0,39-1,06)	*	*
Becker et al.(143)	2009	USA	77,52	31	48	0,9 (0,48-1,67)	*	*
Dal et al.(152)	2005	USA	66,8	0	40	0.870 (0,46-1,64)	*	*
Dal et al.(152)	2005	USA	64	100	67	0,58 (0,32-1,04)	*	*
Harwood et al.(251)	1999	USA	77,8	64	392	1.500 (1-2,3)	*	*
Harwood et al.(251)	1999	USA	73,75	67	188	0,70 (0,37-1,26)	*	*
Wu et al.(252)	2003	China	*	*	301	1,971 (1,09-3,5)	*	*
Brayne et al.(253)	1998	UK	*	68	18	0,78 (0,38-1,65)	*	*
Mendez et al.(254)	1992	USA	*	55	407	0,94 (0,02-54,26)	*	*
French et al.(255)	1985	USA	*	0	78	0,93 (0,41-2,09)	*	*
Kokmen et al.(256)	1991	USA	*	*	415	0,7 (0,38-1,3)	*	*
Li et al.(670)	1992	China	65,3	53	70	0,7 (0,35-1,4)	*	*
Ruitenberg et al.(267)	2001	USA	69,7	30	107	*	0,9 (0,72-1,13)	*
Shah et al.(268)	2006	Sweden	75	*	151	*	1 (0,99-1,01)	*
Foroughan et al.(257)	2008	Iran	70	43	115	1,712 (1,08-2,7)	*	*
Roberts et al.(258)	2006	USA	*	100	264	1,07 (0,71-1,63)	*	*

	Year[1]	Country[2]	Age[3]	Women[4]	n AD[5]	SBP[6]	DBP[7]	SBP and DBP[8]
Kondo et al.(259)	1994	Japan	*	*	60	1,5 (1,10-2,1)	*	*
Suhanov et al.(260)	2006	Russia	69,25	72	260	1,8 (1-10,3)	*	*
Kivipelto et al.(671)	2005	Karelia	*	963	1497	1.57 (0.77-0.17)	*	*
Joas et al.(264)	2012	Sweden	45	100	79	4,92 (1,35-8,48)	*	*
Stewart et al.(269)	2009	Japanese	40-44	*	0	*	*	0,89 (0,57-1,40)
Qiu et al.(672)	2003	Sweden	>75	*	75	*	*	1,24 (0,85-1,83)
Treiber et al.(270)	2008	USA	>60	*	65	*	*	1,18 (0,90-1,54)
Hassing et al.(271)	2009	Sweden	>45-65	*	36	*	*	0,84 (0,64-1,09)
Tsolaki et al.(262)	1997	Greek	*	54	65	0,46 (0,31-0,67)	*	*
Graves et al.(261)	1990	USA	*	68	18	0,5 (0,23-1,07)	*	*
Imfeld et al.(263)	2012	UK	*	69	7086	0,68 (0,63-0,73)	*	*

Note:
1 Year
2 Country
3 Age
4 % Women
5 Sample: AD: AD cases
6 SBP: Systolic Blood Pressure. CI: 95% confidence interval; RR: Risk Ratio
7 DBP: Diastolic Blood pressure. CI: 95% confidence interval; RR: Risk Ratio
8 SBP: Systolic Blood Pressure; DBP: Diastolic Blood pressure. CI: 95% confidence interval; RR: Risk Ratio

ANEXO 3/APPENDIX 3

PRISMA-SChecklist

Tabla A 4. PRISMA Checklist of included studies

Section/topic	#	Checklist item	Location(s) Reported
INFORMATION SOURCES AND METHODS			
Database name	1	Name each individual database searched, stating the platform for each.	Web of Science, Scopus, PubMed, Elsevier Science Direct, and Google Scholar
Multi-database searching	2	If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched.	-
Study registries	3	List any study registries searched.	448
Online resources and browsing	4	Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done.	-
Citation searching	5	Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies).	-
Contacts	6	Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others.	-
Other methods	7	Describe any additional information sources or search methods used.	-
SEARCH STRATEGIES			
Full search strategies	8	Include the search strategies for each database and information source, copied and pasted exactly as run.	We used some key search terms including "stroke", "microvascular infarcts", "dementia", "meta-analysis", "Alzheimer's disease" and "AD".

Section/topic	#	Checklist item	Location(s) Reported
Limits and restrictions	9	Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use.	No initial publication date was set.
Search filters	10	Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used.	-
Prior work	11	Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s).	-
Updates	12	Report the methods used to update the search(es) (e.g., rerunning searches, email alerts).	Email alerts
Dates of searches	13	For each search strategy, provide the date when the last search occurred.	03/22
PEER REVIEW			
Peer review	14	Describe any search peer review process.	Independent researchers in the relevant research area assess submitted manuscripts for originality, validity and significance to help editors determine whether a manuscript should be published in their journal.
MANAGING RECORDS			
Total Records	15	Document the total number of records identified from each database and other information sources.	A total of 448 studies were identified in the search: 68 in ISI Web of Science, 135 in Scopus, 49 in PubMed, 194 in Elsevier Science Direct, and 2 in Google Scholar
Deduplication	16	Describe the processes and any software used to deduplicate records from multiple database searches and other information sources.	Data deduplication software analyzes data to identify duplicate byte patterns. Data Deduplication compilación del SO 14393.1532

Note: PRISMA-S: An Extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews
Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB, PRISMA-S Group.
Last updated February 27, 2020.

Tabla A 5. Key characteristics of included studies investigating the association between prevalent stroke and incident of AD

Study	Year	Country	Mean age ad	Female %	n ad	N	Effect Measure (OR)	LLIC	ULIC	MA	Stroke type
Brayne et al.(333)	2009	England	90.7	21.2	51	100	1.90	0.869	4.153	Cao 2017	IS
Strozyk et al.(334)	2011	USA	84.4	65.3	47	258	1.10	0.409	2.962	Cao 2017	IS
Strozyk et al.(334)	2011	USA	84.4	65.3	84	143	1.50	0.621	3.623	Cao 2017	IS
Troncoso et al.(335)	2008	USA	86.9	68	79	179	4.00	2.025	7.899	Cao 2017	IS
Qiu et al.(265)	2010	Sweden	81.5	75	303	2.212	0.82	0.506	1.316	Zhou 2015	IS
Pareja et al.(336)	2008	Spain	65	65	184	3.864	4.47	2.784	7.184	Zhou 2015	IS
Hayden et al.(244)	2006	USA	74	65	121	3.215	6.44	3.679	11.266	Zhou 2015	IS
Lindsay et al.(242)	2002	Canada	65	65	83	4.236	1.54	0.884	2.682	Zhou 2015	IS
Epstein et al.(337)	2012	USA	75.4	47.8	186	435	1.39	0.418	4.597	Pinho, 2021	HS
Brayne et al.(333)	2009	England	90.7	21.2	51	201	1.50	0.500	4.500	Cao 2017	HS
Honig et al. (338)	2003	USA	79	32	98	1.766	1.83	1.140	2.950	Pinho, 2021	HS
Suter et al.(339)	2002	England	78	41	79	105	4.83	1.135	20.560	Pinho, 2021	MI
Arvanitakis et al.(340)	2011	USA	88.7	35	192	233	4.01	2.689	5.979	Cao 2017	MI
Sonnen et al.(341)	2007	USA	88.7	44	47	258	1.13	0.410	3.115	Cao 2017	MI

Note: AD: Alzhiemer's disease; OR: odds ratio; LLIC, Lower Limit confidence interval; ULIC, Upper Llimit confidence interval; MA: meta-analysis

ANEXO 4/APPENDIX 4

ESTADÍSTICOS DESCRIPTIVOS DE DATOS GENERALES

Se trata del tipo de muestreo de conveniencia, técnica no probabilística, donde las personas que participaron en el estudio se seleccionaron por la disponibilidad para participar en el mismo.

La muestra está conformada por 508 hombres y 947 mujeres (Figura A1). Un total de 1.455 usuarios. La recogida de la muestra se produjo entre las fechas octubre del 2008 y octubre de 2020 en una residencia de personas mayores de la capital de Burgos.

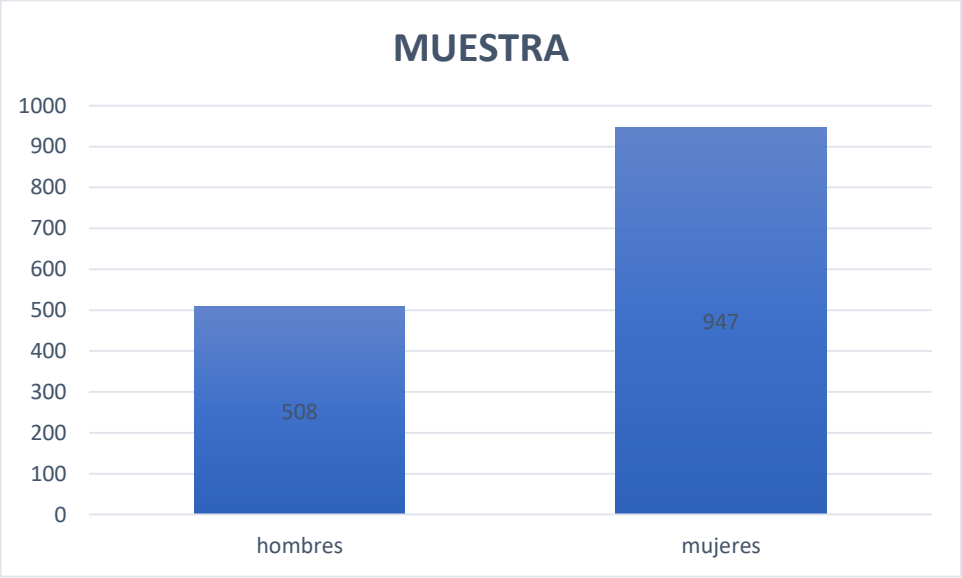

Figura A 1. Muestra por sexo (Fuente: Elaboración propia)

En cuanto a la edad media del total de la muestra son 85.48 años, (Tabla A6) para hombres es inferior, situándose en 83.69 y para la mujer es superior a la media, con un valor de 86.44 (Tabla A6). Los mínimos de edad de participación en el estudio son de 60 (Total de la muestra y hombres) y 62 años para mujeres. Los valores máximos de edad son de 106 años (Total de la muestra y mujeres) y 105 años para los hombres (Tabla A6).

Tabla A 6. Estadísticos descriptivos en relación con la edad (Fuente: Elaboración propia)

Edad	**Hombres**	**Mujeres**	**Total**
Media	83,69	86,44	85,48
Error típico	0,39	0,24	0,21
Mediana	85	87	86
Moda	89	89	89
Desviación estándar	9,00	7,39	8,09
Varianza de la muestra	81,09	54,63	65,54
Curtosis	-0,33	0,59	0,28
Coeficiente de asimetría	-0,48	-0,55	-0,60
Rango	45	44	46
Mínimo	60	62	60
Máximo	105	106	106
Total muestra	508	947	1455

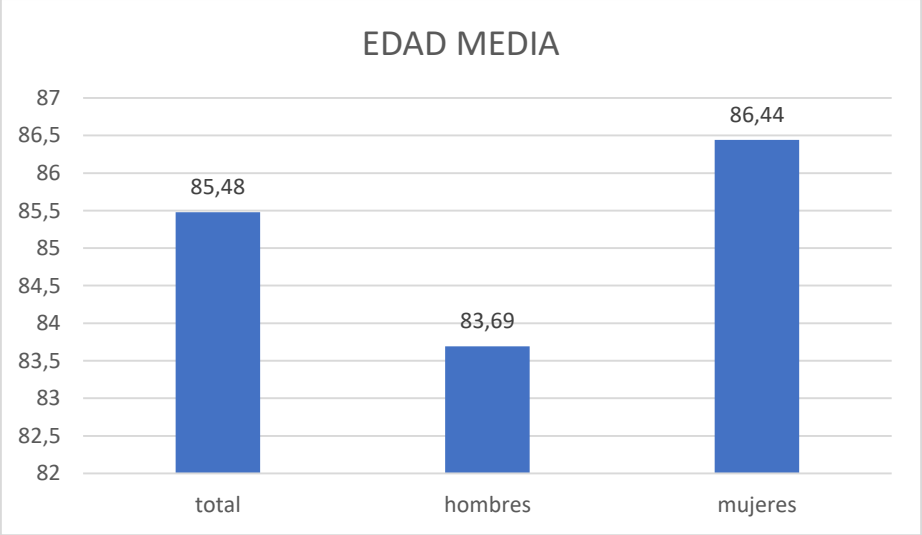

Figura A 2. Edad media de la muestra (Fuente: Elaboración propia)

En la siguiente tabla (Figura A2) se muestran los datos referentes a la muestra agrupados por sexo, tipología de la plaza y estado civil de manera conjunta.

Tabla A 7. Estadísticos descriptivos en relación con la edad (Fuente: Elaboración propia)

Estado civil y tipología plaza	Hombre	Mujer	Total
Casado/a	257	202	459
Centro de Día	47	29	76
I Asistido Grave	44	39	83
I Asistido Leve	38	37	75
I Asistido Moderado	59	38	97
II Asistido	26	19	45
Válido	43	40	83
Divorciado/a	13	13	26
Centro de Día	1	1	2
I Asistido Grave		2	2
I Asistido Leve	5	1	6
I Asistido Moderado	2	4	6
Válido	5	5	10
Separado/a	3	1	4
I Asistido Leve	1		1
Válido	2	1	3
Soltero/a	74	151	225
Centro de Día	4	7	11
I Asistido Grave	12	22	34
I Asistido Leve	13	38	51
I Asistido Moderado	16	39	55
II Asistido	1	12	13
Válido	28	33	61
Viudo/a	161	580	741
Centro de Día	17	75	92
I Asistido Grave	25	104	129
I Asistido Leve	37	117	154
I Asistido Moderado	35	154	189
II Asistido	11	32	43
Válido	36	98	134
Total general	**508**	**947**	**1455**

En la Tabla A8 se pueden observar los valores correspondientes al estado civil agrupados por sexo. La Figura A3 muestra el estado civil de la población total, la Figura A4 el estado civil de la población femenina y la Figura A5, de la población masculina.

Tabla A 8. Estadísticos descriptivos en relación con el estado civil (Fuente: Elaboración propia)

Estado civil	**Hombre**	**Mujer**	**Total**
Casado/a	257	202	459
Divorciado/a	13	13	26
Separado/a	3	1	4
Soltero/a	74	151	225
Viudo/a	161	580	741
Total general	**508**	**947**	**1455**

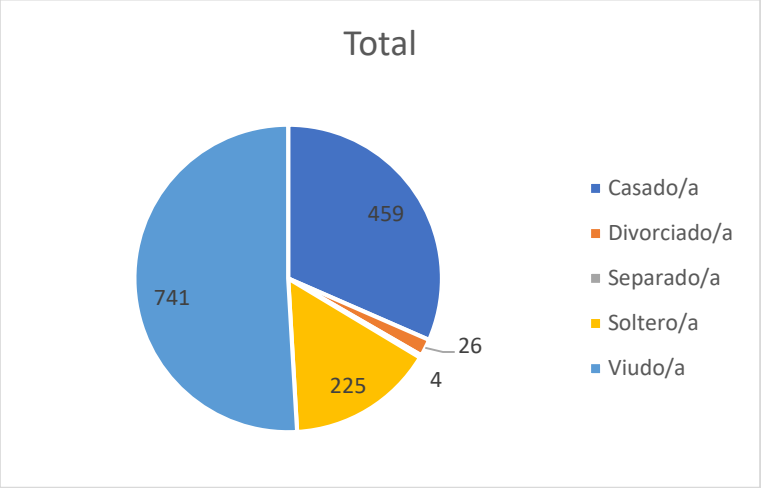

Figura A 3. Muestra total en relación con el estado civil (Fuente: Elaboración propia)

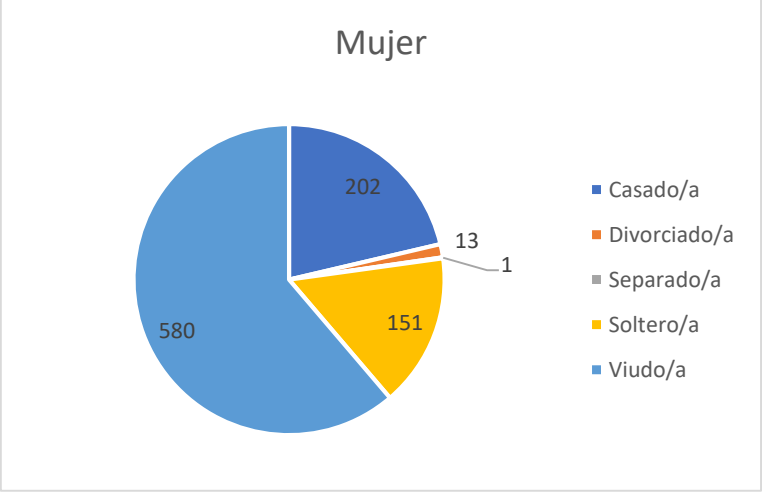

Figura A 4. Estado civil de la población femenina (Fuente: Elaboración propia)

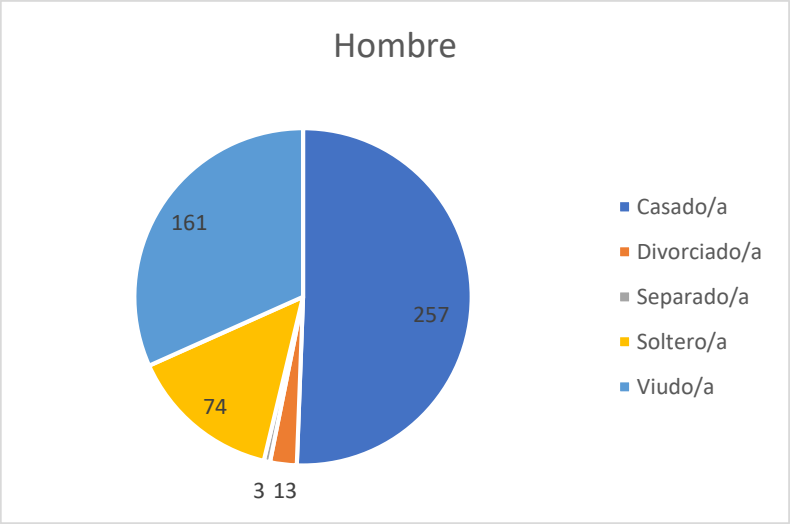

Figura A 5. Estado civil de la población masculina (Fuente: Elaboración propia)

En la Tabla A9 se pueden observar los valores correspondientes a la tipología de la plaza agrupado por sexo.

La Figura A6 muestra la tipología de la plaza de la población total, Figura A7, la tipología de la plaza de la población femenina y la Figura A8, la tipología de la plaza de la población masculina.

Tabla A 9. Estadísticos descriptivos en relación con la tipología de la plaza (Fuente: Elaboración propia)

Tipología plaza	Hombre	Mujer	Total
Centro de Día	69	112	181
I Asistido Grave	81	167	248
I Asistido Leve	94	193	287
I Asistido Moderado	112	235	347
II Asistido	38	63	101
Válido	114	177	291
Total general	**508**	**947**	**1455**

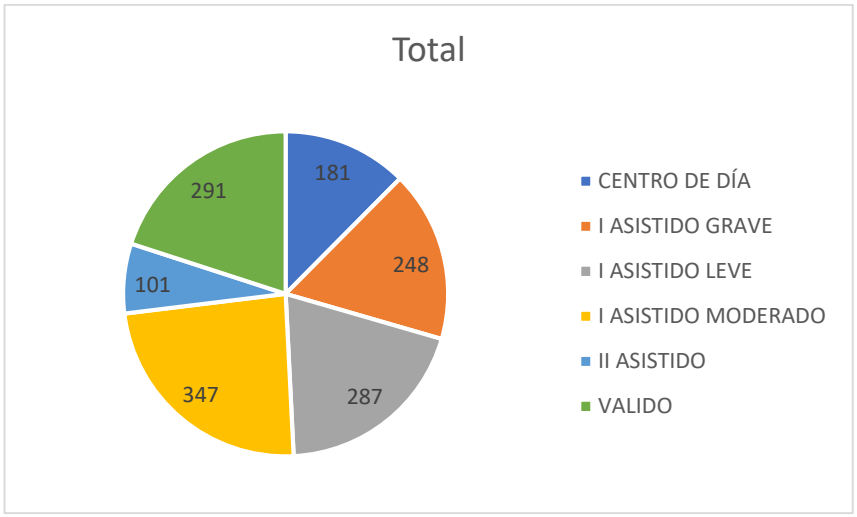

Figura A 6. Tipología de la plaza en la muestra total (Fuente: Elaboración propia)

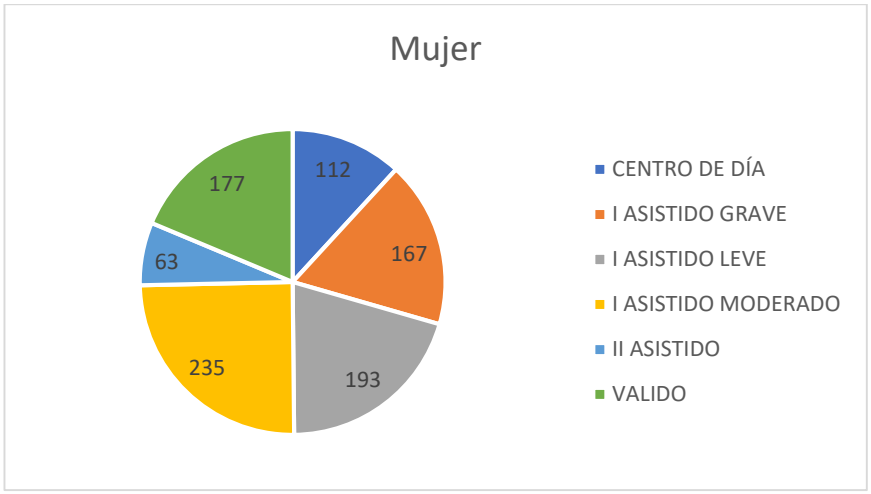

Figura A 7. Tipología de la plaza en la muestra femenina (Fuente: Elaboración propia)

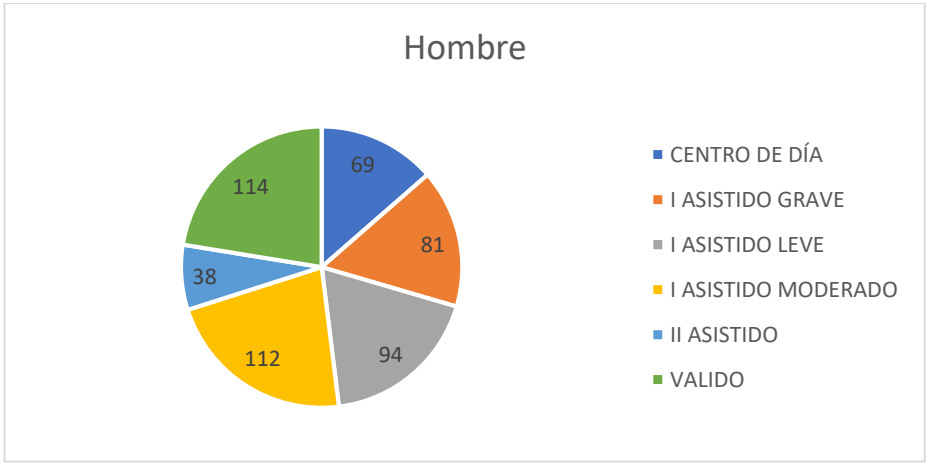

Figura A 8. Tipología de la plaza en la muestra masculina (Fuente: Elaboración propia)

ESTADÍSTICOS DESCRIPTIVOS DE LA MUESTRA EN SIGNOS VITALES Y DE MEDICIÓN CORPORAL

Los signos vitales indican el estado funcional de los usuarios, y se consideran herramientas valiosas para determinar problemas en el organismo, ya que una alteración en cualquiera de ellos supone una patología de base.

Es la onda pulsátil de la sangre, originada en la contracción del ventrículo izquierdo del corazón y que resulta en la expansión y contracción regular del calibre de las arterias. La onda pulsátil representa el rendimiento del latido cardiaco, que es la cantidad de sangre que entra en las arterias con cada contracción ventricular y la adaptación de las arterias, o sea, su capacidad de contraerse y dilatarse (673).

El pulso periférico se palpa fácilmente en pies, manos, cara y cuello. Realmente puede palparse en cualquier zona donde una arteria superficial pueda ser fácilmente comprimida contra una superficie ósea (673).

La velocidad del pulso (latidos por minuto) corresponde a la frecuencia cardiaca, la cual varía con la edad, sexo, actividad física, estado emocional, fiebre, medicamentos y hemorragias (673).

Tabla A 10. Valores descriptivos recogidos en la muestra con referencia a la frecuencia cardíaca (Fuente: elaboración propia)

Frecuencia cardíaca	
Media	76,1
Error típico	0,33
Mediana	76
Moda	70
Desviación estándar	12,77
Varianza de la muestra	163,27
Curtosis	-0,30
Coeficiente de asimetría	0,11
Rango	82
Mínimo	41
Máximo	123
Suma	110812
Cuenta	1455

Los valores normales para la constante vital de frecuencia cardíaca son: recién nacidos (Entre 120-170 pulsaciones por minuto); niños de 2 a 4 años entre 100 y 120; los niños de 6 a 8 años entre 100 y 115 pulsaciones por minuto y en personas adultas oscilan entre 60 y 80. En la Tabla A10 se pueden ver los valores descriptivos recogidos en la muestra con referencia a la frecuencia cardíaca.

El índice de masa corporal se deriva de las medidas de peso corporal y estatura, se calcula con la fórmula Peso/Talla2 (674).

Se plantea que en un Índice de masa corporal (IMC) de 18,5Kg/metros cuadrados o menos, define deficiencia energética crónica; de 25 a 29, 9 Kg /metros cuadrados, indica sobrepeso y mayor o igual a 30 obesidad (675).

En la Tabla A11 se muestran los valores con referencia al peso de la muestra y en la Tabla A12, los valores en relación con la talla. En la Tabla A13, se muestran los valores que corresponden al IMC de la población estudiada.

Tabla A 11. Valores descriptivos recogidos en la muestra con referencia al peso (Elaboración propia)

Peso	
Media	61,7718694
Error típico	0,33710196
Mediana	60,7
Moda	55
Desviación estándar	12,8585731
Varianza de la muestra	165,342903
Curtosis	0,58013839
Coeficiente de asimetría	0,57419096
Rango	79,3
Mínimo	31,7
Máximo	111
Suma	89878,07
Cuenta	1455

Tabla A 12. Valores descriptivos recogidos en la muestra con referencia a la talla (Fuente: elaboración propia)

Talla	
Media	162,60
Error típico	0,21
Mediana	165
Moda	165
Desviación estándar	8,28
Varianza de la muestra	68,65
Curtosis	-0,25
Coeficiente de asimetría	-0,61
Rango	39
Mínimo	141
Máximo	180
Suma	236591
Cuenta	1455

El estudio que analizó la prevalencia de obesidad en España (676) mostró que en la población mayor de 65 años esta prevalencia experimenta un incremento significativo en relación con edades más jóvenes hasta el umbral de los 75 años. La prevalencia de obesidad (IMC igual o mayor de 30 kg/m2) en la población mayor de 65 años se estima en un 35% (un 30,9% en varones y un 39,8% en mujeres).

Tabla A 13. Valores descriptivos recogidos en la muestra con referencia al Índice de Masa Corporal (IMC) (Fuente: elaboración propia)

IMC	
Media	23,53
Error típico	0,14
Mediana	22,99
Moda	25,96
Desviación estándar	5,40
Varianza de la muestra	29,17
Curtosis	0,74
Coeficiente de asimetría	0,65
Rango	34,60
Mínimo	11,53
Máximo	46,12
Suma	34236,23
Cuenta	1455,00

En ancianos institucionalizados se estimó una prevalencia de obesidad del 21% (un 20,5% en varones y un 21,7% en mujeres). El control glucémico de los pacientes diabéticos deberá estar encaminado a tener glucemias de ayuno < 120 mg/dl (< 6.6 mmol/L) y hemoglobina glucosilada < 7%11-14 (677). En la Tabla A14 se muestran las pruebas de glucemia basal registradas en la muestra.

Tabla A 14. Valores descriptivos recogidos en la muestra con referencia a la glucemia basal (Fuente: elaboración propia)

Glucemia Basal	
Media	132,04
Error típico	1,32
Mediana	122
Moda	118
Desviación estándar	45,34
Varianza de la muestra	2056,53
Curtosis	9,44
Coeficiente de asimetría	2,35
Rango	422
Mínimo	45
Máximo	467
Suma	154494
Cuenta	1170

El cuerpo humano necesita consumir una determinada cantidad de oxígeno para el metabolismo de sus células, ese oxígeno se obtiene directamente de la atmósfera durante la inspiración (264).

Los valores típicos de Saturación de oxígeno oscilan entre el 95% y 97% con un rango de variación del 2%. Valores por debajo del 90% se asocian con situaciones patológicas e insuficiencia respiratoria (642) (Tabla A15).

Tabla A 15. Valores descriptivos recogidos en la muestra con referencia a la saturación (Fuente: elaboración propia)

Saturación	
Media	94,41
Error típico	0,06
Mediana	95
Moda	94
Desviación estándar	2,61
Varianza de la muestra	6,83
Curtosis	13,22
Coeficiente de asimetría	-2,30
Rango	29
Mínimo	71
Máximo	100
Suma	137377
Cuenta	1455

La tensión arterial consiste en la presión que ejerce la sangre sobre las paredes arteriales cuando circula por las arterias en el organismo. Como la sangre se mueve por ondas, se pueden dar dos tipos de medidas de tensión o presión arterial: la tensión sistólica, que es la presión de la sangre debida a la contracción de los ventrículos, es decir, la presión máxima; y la tensión diastólica, que es la presión que queda cuando los ventrículos se relajan; ésta es la presión mínima(673). En la Tabla A16 se muestran los valores normales de tensión arterial (673) que pueden ser medidos y en la siguiente tabla (Tabla A17) se muestran los valores de tensión sistólica y diastólica recogidos en la muestra poblacional medida.

Tabla A 16. Valores normales de tensión arterial

Edad	**Presión Sistólica (mmHg)**	**Presión Diastólica (mmHg)**
Lactante	60-90	30-62
2 años	78-112	48-78
8 años	85-114	52-85
12 años	95-135	58-88
Adulto	100-140	60-90

Tabla A 17. Valores descriptivos recogidos en la muestra con referencia a la tensión arterial (Fuente: elaboración propia)

Tensión arterial			
Sistólica		**Diastólica**	
Media	130,76	Media	74,37
Error típico	0,58	Error típico	0,31
Mediana	130	Mediana	74
Moda	140	Moda	70
Desviación estándar	22,26	Desviación estándar	11,94
Varianza de la muestra	495,55	Varianza de la muestra	142,79
Curtosis	0,80	Curtosis	0,37
Coeficiente de asimetría	0,53	Coeficiente de asimetría	0,05
Rango	161	Rango	92
Mínimo	69	Mínimo	30
Máximo	230	Máximo	122
Suma	190256	Suma	108220
Cuenta	1455	Cuenta	1455

La temperatura consiste en el equilibrio entre la producción de calor por el cuerpo y su pérdida. Cuando la temperatura sobrepasa el nivel normal se activan mecanismos como vasodilatación, hiperventilación y sudoración que promueven la pérdida de calor. Si por el contrario, la temperatura cae por debajo del nivel normal se activan mecanismos como aumento del metabolismo y contracciones espasmódicas que producen los escalofríos(673).

Los valores normales de temperatura son: recién nacidos entre 36.1ºC y 37.7ºC; lactante 37.2ºC; niños de 2 a 8 años 37ºC y adultos entre 36ºC y 37ºC. En la Tabla A18 se muestran los valores descriptivos correspondientes a la medición de la temperatura de los usuarios.

Tabla A 18. Valores descriptivos recogidos en la muestra con referencia a la temperatura (Fuente: elaboración propia)

Temperatura	
Media	35,91
Error típico	0,01
Mediana	36
Moda	36
Desviación estándar	0,60
Varianza de la muestra	0,36
Curtosis	0,85
Coeficiente de asimetría	-0,07
Rango	4,6
Mínimo	34,1
Máximo	38,7
Suma	52260,1
Cuenta	1455

ESTADÍSTICOS DESCRIPTIVOS DE LA MUESTRA: HÁBITOS

El tabaquismo constituye un importante problema de salud pública, siendo una de las principales causas de morbimortalidad evitable y prematura(678). En España, el 24% de la población fuma diariamente (679). En la Tabla A19 se muestran los datos de tabaquismo en la muestra analizada. En la Figura A9 se muestran los porcentajes correspondientes al hábito de tabaquismo.

Tabla A 19. Valores correspondientes al hábito de tabaquismo (Fuente: elaboración propia)

Tabaco	**Hombre**	**Mujer**	**Total**
Sí que fuma	46	37	83
No fuma	462	910	1372
Total general	**508**	**947**	**1455**

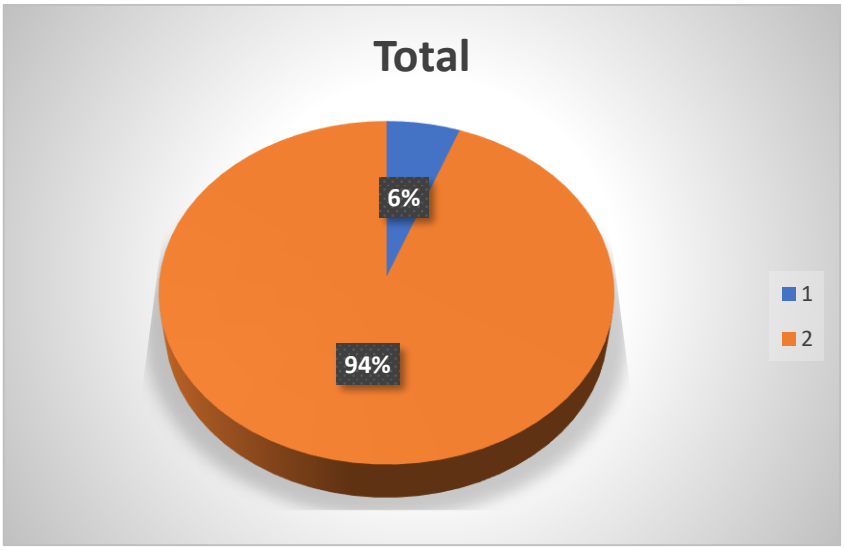

Figura A 9. Porcentajes correspondientes al hábito de tabaquismo (Fuente: elaboración propia)

La prevalencia de bebedores diarios en España es menor que la de fumadores (12,9%), y es una de las más bajas de la Unión Europea (679). En relación con los estilos de vida, los resultados del estudio realizado por Zaragoza et al. (680) mostraron un mayor consumo de alcohol y de tabaco en hombres que en mujeres. En la muestra analizada es mayor el consumo de tabaco en hombres, pero no el consumo de alcohol, ya que como se observa en la siguiente Tabla A20, es mayor en las mujeres. En Figura A10 se muestran los porcentajes correspondientes al hábito de consumo de alcohol.

Tabla A 20. Valores correspondientes al hábito de consumo de alcohol (Fuente: elaboración propia)

Alcohol	**Hombre**	**Mujer**	**Total**
Sí que bebe	47	109	156
No bebe	461	838	1299
Total general	**508**	**947**	**1455**

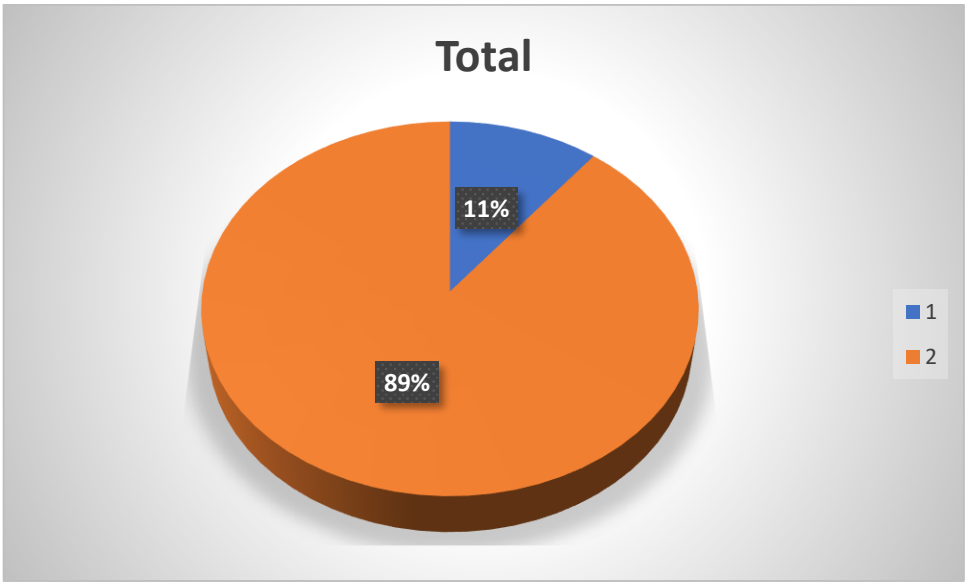

Figura A 10. Porcentajes correspondientes al hábito de consumo de alcohol (Fuente: elaboración propia)

En el estudio realizado por Matilla-Mora et al. (70) se demuestra la eficacia y efectividad de la terapia ocupacional en el retraso de la progresión de las distintas disfunciones, especialmente cuando se utilizan programas estructurados de terapia ocupacional domiciliaria.

En la siguiente Tabla A21 se muestra la asistencia a terapias cognitivas en el programa de intervención de Terapia Ocupacional y en la Figura A11 los porcentajes relativos a la asistencia diaria a terapias cognitivas.

Tabla A 21. Valores correspondientes a la asistencia diaria a terapias cognitivas (Fuente: elaboración propia)

Terapias Cognitivas	**Hombre**	**Mujer**	**Total**
Sí que asiste	397	754	1151
No asiste	111	193	304
Total general	**508**	**947**	**1455**

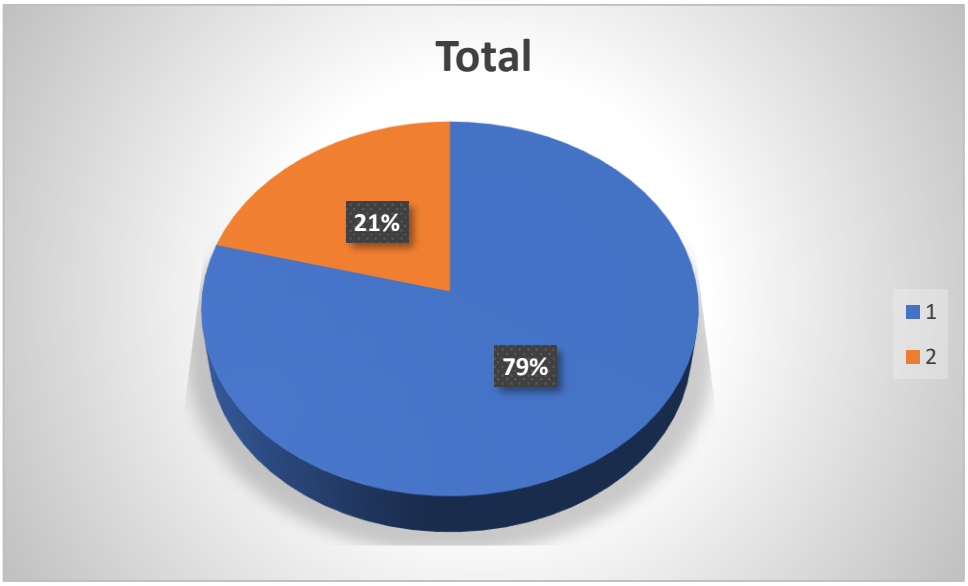

Figura A 11. Porcentajes correspondientes a la asistencia diaria a terapias cognitivas (Fuente: elaboración propia)

Para mejorar aspectos como el desempeño de las actividades de la vida diaria, se deben realizar programas que incluyan ejercicios aeróbicos y de fortalecimiento, estimulación cognitiva y sensorial y entrenamiento de memoria (70). En la siguiente Tabla A22, se muestra la asistencia por sexo a las terapias físicas realizadas en el departamento de Terapia Ocupacional. En la Figura A12 se muestran los porcentajes relativos a la asistencia diaria a terapias físicas.

Tabla A 22. Valores correspondientes a la asistencia diaria a terapias físicas (Fuente: elaboración propia)

Terapias Físicas (TO)	**Hombre**	**Mujer**	**Total**
Sí que asiste	453	855	1308
No asiste	55	92	147
Total general	**508**	**947**	**1455**

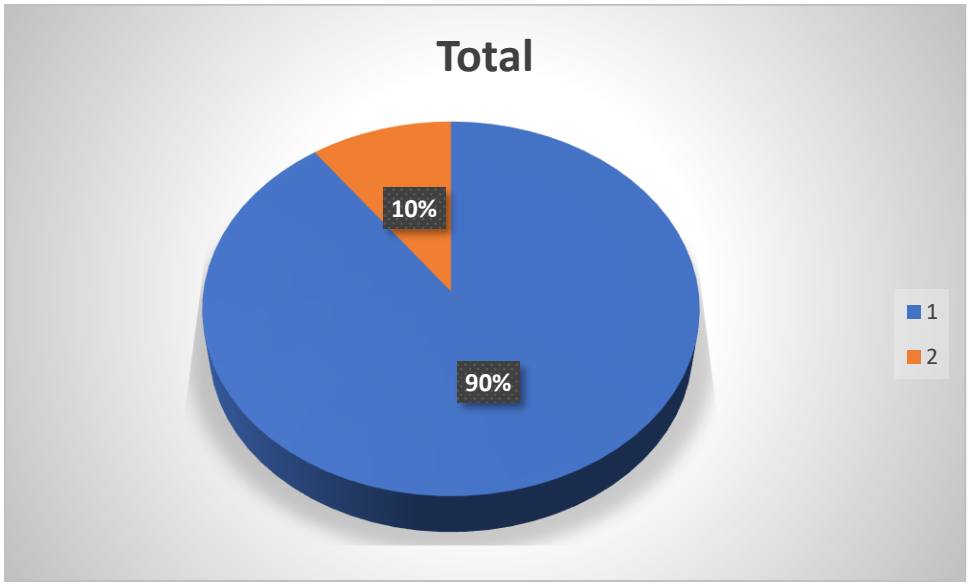

Figura A 12. Porcentajes correspondientes a la asistencia diaria a terapias físicas (Fuente: elaboración propia)

ESTADÍSTICOS DESCRIPTIVOS DE LA MUESTRA: MEDICAMENTOS

La clasificación Anatómica Terapéutica Química (ATC) consiste en un sistema europeo de codificación de sustancias farmacéuticas y medicamentos en cinco niveles con arreglo al sistema u órgano efecto y al efecto farmacológico, las indicaciones terapéuticas y la estructura química de un fármaco(471). De esta manera a cada medicamento le corresponde un código ATC, y a su vez este código se especifica en una ficha técnica (donde aparecen resumidas las características del producto) del medicamento(472).

La clasificación ATC se estructura en cinco niveles(471):

- **1.er nivel (anatómico):** órgano o sistema sobre el que actúa el fármaco (existen 14 grupos en total).
- **2.o nivel:** subgrupo terapéutico.
- **3.er nivel:** subgrupo terapéutico o farmacológico.
- **4.o nivel:** subgrupo terapéutico, farmacológico o químico.

- **5.o nivel:** nombre del principio activo (mono fármaco) o de la asociación medicamentosa

En la clasificación cada nivel o categoría se distingue mediante una letra y un número o una serie de letras y números. En este sistema de clasificación, todos los preparados a base de un mismo y único fármaco reciben un código idéntico(471).

Los medicamentos que se recogen en la muestra están divididos conforme al tercer nivel, de manera que se han creado subgrupos farmacológicos de clasificación de los distintos medicamentos atendiendo al tercer nivel de la codificación farmacológica ATC. En la Tabla A23, se pueden observar la clasificación de los medicamentos.

Tabla A 23. Clasificación ATC de medicamentos. Fuente: Elaboración propia

Clasificación ATC de Medicamentos **Clasificación ATC**	**Número ATC**
Agentes antitrombóticos	13
Agentes contra el estreñemiento	7
Agentes contra las úlceras pépticas y el RGE	2
Agentes contra padecimientos funcionales del estómago e intestino	4
Agentes contra padecimientos obstructivos de las vías respiratorias	60
Agentes modificadores de los lípidos	27
Alimentos y dietéticos	66
Analgésicos	45
Anestésicos	44
Ansiolíticos	49
Antiácidos	3
Antiarrítmicos	18
Antibacterianos	33
Antidepresivos	51
Antidiabéticos	11
Antidiarreicos, antiinfecciosos y antiinflamatorios intestinales	8
Antieméticos y antinauseosos	5
Antiepilépticos	46
Antigotosos	42
Antihemorrágicos	14
Antihipertensivos	21
Antihistamínicos	62
Antiinflamatorios y antirreumáticos	40
Antimicobacterias	35
Antimióticos	34

Clasificación ATC de Medicamentos Clasificación ATC	Número ATC
Antineoplásicos e inmunomoduladores	39
Antiparasitarios, insecticidas y repelentes	57
Antiparkinsonianos	47
Antipsicóticos	48
Antivirales	36
Betabloqueantes	25
Bloqueantes de canales del calcio/Agentes activos sobre el sistema renina angiotensina	26
Corticoesteroides	31
Dermatológicos	28
Digestivos, incluidos enzimas	10
Diuréticos	22
Estimulantes cardíacos	19
Fármacos antidemencia	53
Fármacos usados en desórdenes adictivos	55
Glucosálidos digitálicos	17
Hipnóticos/Sedantes	50
Hormonas hipofisarias, hipotalámicas, pancreáticas y homeostásis del calcio	32
Oftalmológicos	63
Otológicos	64
Parasimpático miméticos	56
Preparaciones nasales	58
Preparados antianémicos	15
Preparados antiobesidad	9
Preparados antivértigo	54
Preparados estomatológicos	1
Preparados para el tratamiento de enfermedades óseas	43
Preparados para la garganta	59
Preparados para la tos y el resfriado	61
Psicoestimulantes	52
Relajantes musculares	41
Sistema genitourinario y hormonas sexuales	29
Sueros inmunes e inmunoglobulinas	37
Sustitutos de sangre y solución para perfusión	16
Terapia biliar y hepática	6
Terapia tiroidea	30
Vacunas	38
Varios/Cosméticos	65
Vasodilatadores periféricos	23
Vasodilatadores usados en enfermedades cardíacas	20
Vasoprotectores	24
Vitaminas/Suplementos minerales	12

La clasificación en España se reguló a partir del Real decreto 1348/2003, del 31 de octubre, (681) por el que se adaptó la clasificación anatómica de medicamentos al sistema de clasificación ATC, en el plazo de tres años desde su entrada en vigor, se regulaba que España adaptaría la clasificación de medicamentos a la clasificación de la Unión Europea denominada ATC.

ESTADÍSTICOS DESCRIPTIVOS DE LA MUESTRA: PATOLOGÍAS

La Clasificación Estadística Internacional de Enfermedades y Problemas Relacionados con la Salud (CIE-10) es la Décima Revisión de la Clasificación Internacional de Enfermedades (CIE) que desde 1948 está a cargo de la Organización Mundial de la Salud (OMS) (454). Fue aprobada el 1989 por la OMS con la recomendación de que entrara en vigor el 1 de enero de 1993 (455).

Se ha utilizado la clasificación CIE 10 para clasificar las distintas patologías identificadas en la muestra total. Del total de 1117 patologías, se muestran en la siguiente Tabla A24 las patologías clasificadas en 41 grupos atendiendo a la clasificación internacional (CIE-10).

Tabla A 24. Patologías clasificadas en base a los criterios CIE-10 de la muestra

Patología Clasificadas (41 Grupos) **Grupo CIE 10**	**Nº**
Ciertas enfermedades infecciosas y parasitarias	1
Tumores (neoplasias)	2
Enfermedades de la sangre y de los órganos hemotopoyéticos y ciertos Trastornos que afectan al mecanismo de la inmunidad	3
Enfermedades endocrinas, nutricionales y metabólicas	4
Trastornos mentales y del comportamiento	5
Enfermedades inflamatorias del sistema nervioso central	6
Atrofias sistémicas que afectan principalmente al sistema nervioso central	7
Trastornos extrapiramidales y del movimiento	8
Otras enfermedades degenerativas del sistema nervioso	9
Enfermedades desmielinizantes del sistema nervioso central	10
Trastornos episódicos y parosíxticos	11
Trastornos de los nervios, de las raíces y de los plexos nerviosos	12
Polineuropatías y otros trastornos del sistema nervioso periférico	13
Enfermedades neuromusculares y de la unión neuromuscular	14
Parálisis cerebral y otros síndromes paralíticos	15
Otros trastornos del sistema nervioso	16

Patología Clasificadas (41 Grupos)

Grupo CIE 10	**Nº**
Enfermedades del ojo y sus anexos	17
Enfermedades del oido y de la apófisis mastoides	18
Fiebre reumática aguda	19
Enfermedades cardíacas reumáticas crónicas	20
Enfermedades hipertensivas	21
Enfermedades isquémicas del corazón	22
Enfermedad cardiopulmonar y enfermedades de la circulación pulmonar	23
Otras formas de enfermedad del corazón	24
Enfermedades cerebrovasculares	25
Enfermedades de las arterias y de los vasos capilares	26
Enfermedades de las venas y de los vasos y ganglios linfáticos	27
Otros trastornos del sistema circulatorio	28
Enfermedades del sistema respiratorio	29
Enfermedades del sistema digestivo	30
Enfermedades de la piel y el tejido subcutáneo	31
Enfermedades del sistema osteomuscular y del tejido conjuntivo	32
Enfermedades del sistema genitourinario	33
Embarazo, parto y puerperio	34
Ciertas afecciones originadas en el período neonatal	35
Malformaciones congénitas, deformidades y anomalías cromosómicas	36
Síntomas, signos y hallazgos anormales clínicos y de laboratorio no clasificados en otra parte	37
Traumatismo de la cabeza	38
Otros traumatismos, envenenamientos y algunas otras consecuencias de causa externa	39
Causas externas de morbilidad y mortalidad	40
Factores que influyen en el estado de salud y contacto con los servicios de salud	41

La CIE es una clasificación realizada por una agencia internacional de las Naciones Unidas, un recurso público de libre acceso para servir de herramienta en la salud pública(682,683). CIE-10 es una clasificación orientada a describir morbilidad y causas de muerte. Con sus más de 14.000 códigos es posible codificar la mayoría de los diagnósticos más frecuentes tanto en ámbitos ambulatorios como de internación(138).

ANEXO 5/APPENDIX 5

ARTÍCULOS PUBLICADOS

brain sciences

MDPI

Review

Cholesterol and Alzheimer's Disease Risk: A Meta-Meta-Analysis

Olalla Sáiz-Vazquez [1], Alicia Puente-Martínez [2], Silvia Ubillos-Landa [3,*], Joaquín Pacheco-Bonrostro [4] and Javier Santabárbara [5,6]

1 Department of Occupational Therapy, Faculty of Health Science, University of Burgos, C/Villadiego, 1, 09001 Burgos, Spain; osaiz@ubu.es
2 Department of Social Psychology and Methodology of Behavioral Science, University of the Basque Country, Avenida Tolosa 70, 20018 San Sebastián, Spain; alicia.puente@ehu.es
3 Department of Social Psychology, Faculty of Health Science, University of Burgos, C/Villadiego, 1, 09001 Burgos, Spain
4 Department of Applied Economy, Faculty of Economics and Business Sciences, University of Burgos, Pza. De la Infanta Dª Elena, s/n. 09001 Burgos, Spain; jpacheco@ubu.es
5 Department of Microbiology, Pediatrics, Radiology and Public Health, University of Zaragoza, C/Domingo Miral s/n, 50009 Zaragoza, Spain; jsantabarbara@unizar.es
6 Aragonese Institute of Health Sciences (IIS Aragón), 50009 Zaragoza, Spain
* Correspondence: subillos@ubu.es; Tel.: +34-947-258-074

Received: 25 May 2020; Accepted: 14 June 2020; Published: 18 June 2020

Abstract: Background: Alzheimer's disease (AD) is the most common subtype of dementia. In the last ten years, the relationship between cholesterol and AD has been investigated. Evidence suggests that cholesterol is associated with AD and represents promising targets for intervention. However, the causality of these associations is unclear. Therefore, we sought to conduct a meta-meta-analysis to determine the effect of cholesterol on the development AD. Then, we assessed the effect of serum levels of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC) and triglycerides (TG), on AD risk. Methods: A systematic search of meta-analyses was conducted. Scopus, Web of Science, Science direct, PubMed and Google academic system databases were reviewed. Results: We found 100 primary studies and five meta-analyses to analyze the relationships between cholesterol and AD. The total effect of cholesterol on risk of AD was significant and heterogeneous. Subgroup analysis shows that LDL-C levels influence the development of AD. However, non-significant effects of HDL-C, TC and TG levels on AD were found. Conclusions: These results strengthen the evidence that LDL-C cholesterol levels increase risk for AD. More initiatives to investigate the relationship between cholesterol and AD are needed.

Keywords: Alzheimer's disease; etiology; cholesterol; risk factors; meta-analysis

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder resulting in cognitive impairment. AD is characterized by a gradual decline in memory and other cognitive and executive functions, and the progressive development of affective and behavioral disorders [1]. The onset of AD is insidious, and its progression is gradual. As it progresses, various patterns of deficits are seen, but the disorder most commonly begins with deficits in recent memory, which are followed by aphasia, apraxia and agnosia after several years [2]. AD also may cause psychiatric symptoms and personality changes [3]. At the beginning, it affects some abilities, but in the most severe stages, people may depend entirely on others for basic activities of daily living [2].

The etiology of AD is unknown [4]. With the global population aging, AD has increased considerably and become a primary concern for governments and the scientific and medical communities [5]. In Europe, the AD rate is around 5.05% (3.31% for men and 7.13% for women). The AD increase by age reaches 4% of prevalence worldwide, and it increases to 4.02% in people over 60 years old [6,7]. A recent study indicated that the prevalence of AD in individuals aged 60 to 69 years was 1.9 times higher in females than in males (108 cases versus 56 cases per 10,000 persons) [7]. In Spain, around 400,000 people suffer from AD, with the highest prevalence in central and north-eastern Spain [8].

Disorders of lipid homeostasis are common risk factors for cardiovascular disease, which is linked to AD [9]. Dyslipidemia has been identified as a risk factor for AD [1]. This concept refers to abnormal levels of lipids or lipoproteins in the blood, which include high levels of low-density lipoprotein (LDL-C), low levels of high-density lipoprotein (HDL-C), total cholesterol (TC) and triglycerides (TG) [1]. According to previous results, the overall performance of four independent test results should be considered indexes for the prediction of AD, and provide accurate information on an individual's lipid metabolism status or serum lipid and cholesterol levels [10–12].

In the last ten years, the relationship between cholesterol and AD has been extensively investigated, especially in longitudinal epidemiological studies [10]. Evidence suggests that there is a relationship between having high cholesterol levels in blood in mid- and late-life and the development of dementia [1,13]. Specifically, some studies have demonstrated that dyslipidemia, mainly a high level of LDL-C, has vascular and neurotoxic effects, and is implicated in the pathogenesis of AD [10,14–16]. Additionally, another study indicates that if the TC in the brain membrane increases, synapses are not performed normally and, therefore, affect cognitive degeneration in AD [17]. Nevertheless, other studies did not find an association between hypercholesterolemia (high levels of LDL-C, TC, and TG) and AD [18,19]. Regarding HDL-C levels, Tynkkynen et al. [20] found that high levels of HDL-C were inversely associated with the risk of AD. Other studies share the same finding [21,22]. However, some studies did not find an association between high triglycerides levels and high levels of HDL-Cproteins and AD [1,12,18].

The study of the disorders of lipid homeostasis is essential, because it may reduce the consequences of vascular diseases and neurodegenerative diseases, among others, in a cost-effective way [1]. First, this study aimed to conduct a meta-meta-analysis to determine the global effect of cholesterol on AD risk. Second, as there was no consensus in the previous literature about the impact of different types of cholesterol on AD, the effects of serum levels of LDL-C, HDL-C, TCTG on the development of AD were analyzed.

2. Materials and Methods

2.1. Data Collection

We applied the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses [23]. For data collection, we searched meta-analyses reporting outcomes in individuals with diagnoses of AD. To locate potentially suitable studies, we conducted several searches using 5 electronic databases (last search completed in January 2020), including the Web of Science, Scopus, Pubmed, Science Direct and Google Scholar. No publication date was imposed. The electronic search adopted several combinations of the following keywords: "cholesterol" AND Alzheimer's disease AND meta-analysis. The same search strategy was used in academic Google, but limited to the title. Articles were also searched manually and, if required and when feasible, authors were contacted directly for additional information. The search was also done in the Spanish language.

The study selection included previous meta-analyses that met the following criteria: (1) meta-analysis studies that included measures for cholesterol (LDL-C, HDL-C, TC and TG) and AD diagnosis; (2) they should be written in English or Spanish; (3) quantitative studies that reported effect sizes or data that enabled effect size calculation or estimation; (4) meta-analyses that included human samples.

All abstracts were independently analyzed by 2 researchers. Then, after the exclusion of irrelevant abstracts, all remaining articles were critically inspected to check data accuracy. For meta-analyses that met the inclusion criteria, a third investigator independently extracted the salient data. Data were collected directly from the text, correlation matrixes or other statistical tables from the included studies (see supplemental material).

The primary variable (type of cholesterol), design (cross-sectional or longitudinal studies), country of origin of the study, sample size, gender, mean age, main results and an effect size of the relationships between cholesterol and AD were extracted. Information on all the collected data from the selected studies is presented in Table 1.

2.2. Quality Assessment

Quality of the meta-analyses was independently coded by two co-authors using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) tool [24], which has shown to have good inter-rater agreement, reliability, and content validity [24,25]. Total scores for each meta-analysis were calculated as the sum of the 11 items on a binary scale. Quality classifications were established as low quality (0–4), moderate quality (5–8), and high quality (9–11).

2.3. Statistical Analysis

We conducted meta-meta-analysis, combining standard mean difference (SMD), odds ratio (OR), and risk ratio (RR) for AD reported in the selected meta-analyses [26]. We report separate meta-analytic results for each meta-analysis in Table 1. Additionally, we identified separate effect sizes for LDL-C, HDL-C, TC and TG cholesterol levels and their relationship with AD risk. The most frequently reported measure of the associations with cholesterol was SMD and OR. Hence, the results of this meta-meta-analysis are reported in OR format. For each meta-analysis, we calculated (see Tables 2–5): (a) the 95% confidence interval of the effect; (b) the Z-value and p (two-tailed significance); and (c) k or number of studies [27]. RRs and ORs were considered as equivalent, as deemed appropriate when the outcome condition is relatively rare (incidence < 15%) [28]. Adjusted effect measures were used in the analysis when they were included in the source studies, under the assumption that adjustment was performed to remove bias in the estimate of the association between cholesterol and AD. We conducted a random-effect model that allowed SMD and ORs to be incorporated into the same input. Random-effect models are more appropriate than fixed-effect models when the number of studies included in the meta-analysis is low (< 10) [29].

Initially, we performed an analysis summarizing all the available data into a single pooled estimate [30]. Then, to assess the heterogeneity of our results, subgroup analyses were performed to examine the differential effects of type of cholesterol: (1) LDL-C, (2) HDL-C, (3) TC and (4) TG. We did not assume a common among-study variance component across subgroups.

We calculated summary estimates and plotted the effects, using Comprehensive Meta-Analysis software [31]. The heterogeneity of the results obtained from the different meta-analysis was calculated using the Q statistic. Additionally, the presence of heterogeneity was evaluated by calculating the I^2. The I^2 statistic explains the percentage of variance in the observed effects due to variance in the true effects. I^2 values of 25% are considered as low-heterogeneity, 50% as moderate-heterogeneity, and 75% as high-heterogeneity [30]. Statistical significance was set at $p \leq 0.05$. The effect sizes of the mean differences were estimated using Cohen's criteria [32]. A small effect was conceptualized as $d = 0.20$, medium $d = 0.50$, and large $d = 0.80$.

Regarding the risk of AD and the cholesterol component, the direction of the reported effect size coefficient was reversed wherever necessary, such that all included effect sizes represented the association between cholesterol and an increase in the risk of suffering from AD, instead of a decrease in the AD risk.

3. Results

A total of 331 studies were identified from major databases: 64 in ISI Web of Science (WOS), 141 in Scopus, 45 in PubMed, 79 in the Elsevier Science Direct and two in Google Scholar.

Twenty-two meta-analyses were eligible for inclusion in this meta-meta-analysis. Of these, 17 were excluded because: (a) $k = 2$ did not report an effect size; (b) $k = 2$ did not provide information on the relationship between cholesterol and AD; (c) $k = 6$ were duplicated; (d) $k = 5$ were systematic reviews about other issues; (e) $k = 1$ aimed to study the effect of medication on AD; and (f) one meta-analysis that included the same primary studies as another study (see Figure 1). Finally, a total of $K = 5$ meta-analyses were analyzed in this meta-meta-analysis ($k = 12$ pooled effect sizes), including data from $n = 100$ primary studies ($n = 236$ effect sizes) (see Supplementary Table S1).

Twelve effect sizes were extracted from a total of five meta-analyses. $K = 3$ effect sizes informed about LDL-C and risk of AD (25%); $k = 3$ about HDL-C (25%); $k = 4$ about TC (33.3%), and $k = 2$ of TG (16.7%). Table 1 summarizes the key features of the included primary diagnosis, design, number of primary studies, country of origin of the study, sample size, gender, mean age, results, total scores of quality of included meta-analyses (MAs) (AMSTAR) and effect sizes of the relationships between cholesterol and AD that were extracted.

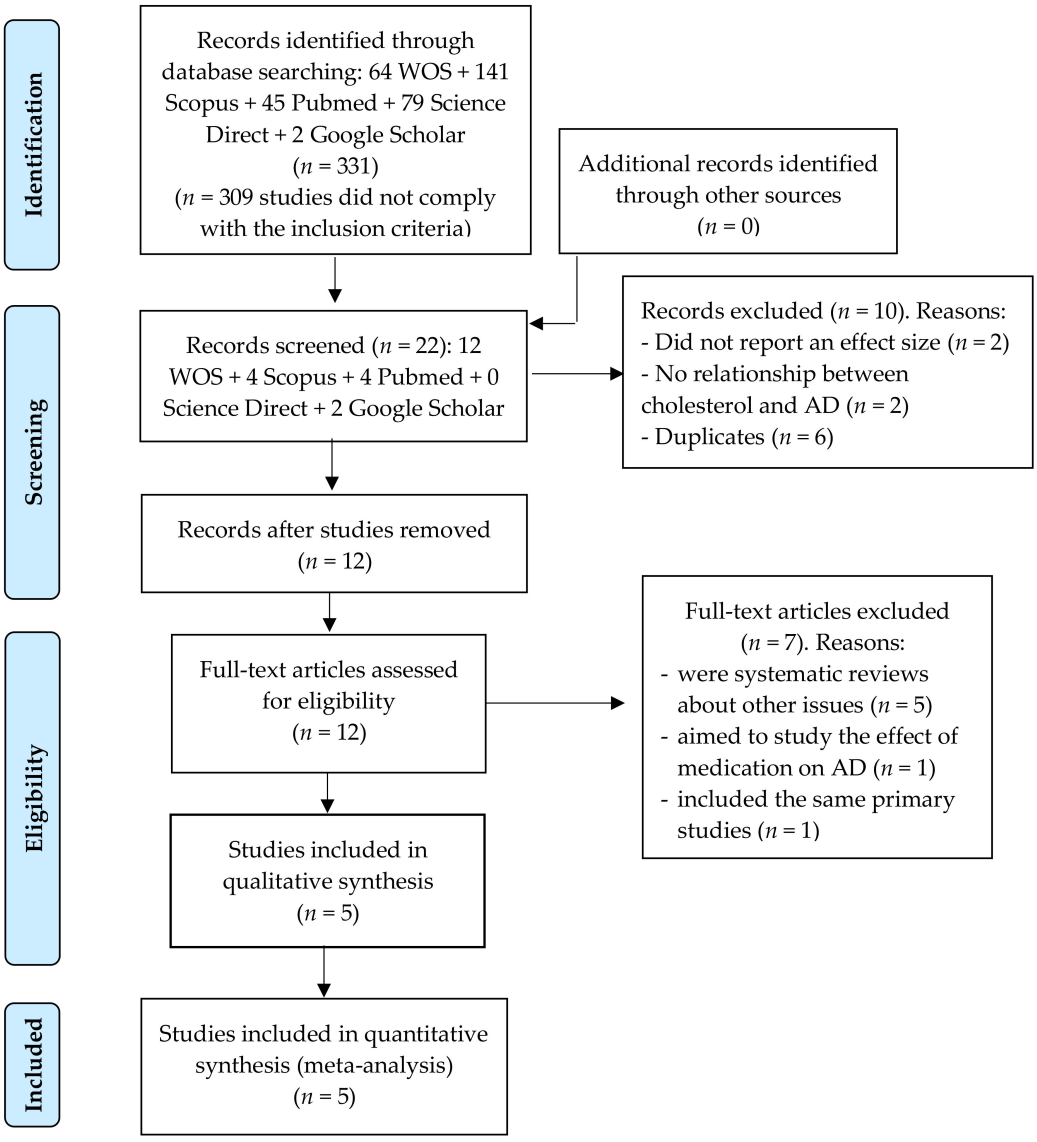

Figure 1. Flow chart depicting the selection of articles for our meta-meta-analysis.

Table 1. Population characteristics in studies of Alzheimer's disease (AD)and cholesterol.

Study	Variable	Total *n*	Design	*K*	Country (*N*)	Sample	% F	Age	Result	Effect Size			AMSTAR Scores
										Effect Size	95% *CI* LL~UL	*p*	
Zhou et al. [33]	LDL-C	AD *n* = 2266 HC *n* = 4767	C	20	EU (7), USA (6), AS (4), AF (2), OC (1)	AD *n* = 2266 HC *n* = 4767	69.50	50-87	> LDL-C > AD	*SMD* = 0.35	0.12~0.58	<0.01	10
Liu et al. [1]	LDL-C	AD *n* = 891 HC *n* = 2399	C	9	EU (3), USA (4), AS (2)	AD *n* = 584 HC *n* = 2130	70	59-92	> LDL-C > AD	SMD = 1.40	0.70~2.10	0.000	11
	HDL-C			11	EU (4), USA (4), AS (3)	AD *n* = 727 HC *n* = 2233			HDL-C = AD	*SMD* = −0.53	−1.12~0.07	0.082	
	TC			13	EU (6), USA (4), AS (3)	AD *n* = 809 HC *n* = 2303			> TC > AD	*SMD* = 0.76	0.13~1.40	0.019	
	TG			6	EU (4), USA (2)	AD *n* = 273 HC *n* = 239			> TG = AD ns.	*SMD* = −0.02	−0.25~0.21	0.859	
Wu et al. [12]	LDL-C	AD *n* = 3037 HC *n* = 5375	C	33	AS (33)	AD *n* = 2843 HC *n* = 5174	53.87	56–84	> LDL-C > AD	*OR* = 1.64	1.07~2.51		10
	HDL-C			33		AD *n* = 2921 HC *n* = 5271			< HDL = AD ns.	*OR* = 0.81	0.55~1.19		
	TC			33		AD *n* = 2661 HC *n* = 5189			> TC > AD	*OR* = 1.58	1.10~2.92		
	TG			28		AD *n* = 2556 HC *n* = 4903			> TG = AD ns.	*OR* = 1.33	0.99~1.79		
Wang et al. [18]	TC	AD *n* = 959 HC *n* = 694	C	16	-	AD *n* = 959 HC *n* = 694	60.21	60–94, *M* = 71.38	> TC = AD	*SMD* = −0.23	0.65~0.19	0.29	10
Xu et al. [13]	HDL-C	AD *n* = 12604 HC *n* = 2,256,519	L(2–9)	6	USA (2), EU (4)	AD *n* = 499 HC *n* = 11,991	56.3	*M* = 71.21	> HDL = AD	*RR* = 1.00	0.86~1.14	0.942	11
	TC		L (3.2–32)	16	USA (8), EU (4), AS (4)	AD *n* = 12275 HC *n* = 2,246,750	49.5	*M* = 68.5	> TC = AD	*RR* = 0.96	0.81–1.11	0.000	

Note: Variables: AD: Alzheimer's disease; LDL-C: low-density level cholesterol; HDL-C: high-density level cholesterol; TC: total cholesterol; TG: triglycerides; Total N of each study; Design: C: cross-sectional; L: longitudinal (year); *K*: number of studies; Country: *N*: number of independent studies. EU: European Union; USA: United States of America; AS: Asia; AF: Africa; OC: Oceania; [6] Independent Sample: AD: Alzheimer´s disease cases; HC: healthy control participants for each type of cholesterol.; F: females; M: mean; *CI*: 95% confidence interval; *SMD*: standard mean difference; *OR*: odds ratio; *RR*: risk ratio.

First, we investigated the relationship between overall cholesterol components and risk of AD in five meta-analyses, with a total of 2,289,511 participants, most of whom were female (*N* cases, AD = 19,757; *N* controls, HCs = 2,269,754). We identified a total of 12 estimates for cholesterol serum lipids (LDL-C, HDL-C, TC, and TG). The distribution of these estimates is shown in Figure 2.

The total random effect of cholesterol on risk of AD was significant with *OR* = 1.29, 95% confidence interval (CI) [1.04, 1.60], $Z = 2.28$, $p = 0.023$, $d = 0.14$. When calculating the overall effect of lipid parameters, evidence of significant heterogeneity was found ($Q = 45.49$, $df = 11$, $p = 0.0001$, $I^2 = 75.82\%$). Therefore, we examined whether subgroup analysis changed the results, as cholesterol levels at onset were significantly associated with AD. Heterogeneity could be explained, due to the different types of cholesterol: LDL-C, HDL-C, TG and TC. The results indicated that there were differences between the types of cholesterol: $Qb = 9.04$, $df = 3$, $p = 0.029$. Hence, independent analyses for each type of cholesterol were performed.

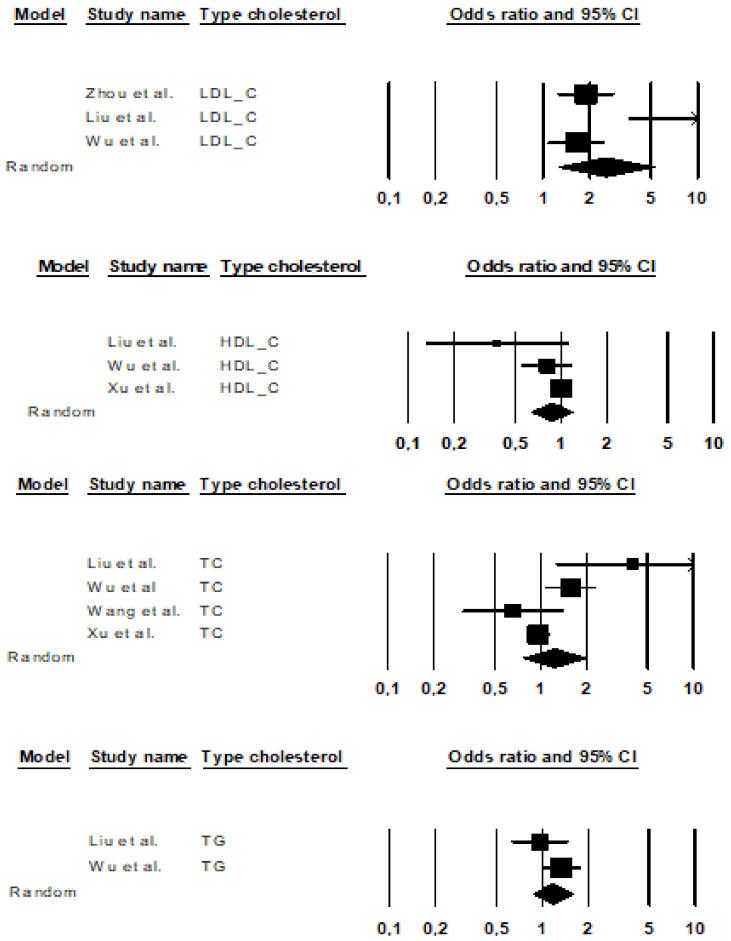

Figure 2. Forest plot of the effects of dyslipidemia on Alzheimer's disease (AD): low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG).

3.1. Studies of LDL-C Levels

The total random effect of LDL-C levels on AD was significant for $k = 3$ meta-analysis ($n = 17{,}764$, $n = 5693$ AD, and $n = 12{,}071$ HCs): $OR = 2.55$, 95% CI [1.25, 5.22], $Z = 2.57$, $p = 0.010$, $d = 0.52$.

The first study conducted by Zhou et al. [33] provided information of $K = 20$ studies that compared serum LDL-C levels in AD and HC subjects ($N = 7033$ participants: 2266 AD and 4767 HCs). Liu et al. [1] also compared AD ($n = 584$ AD) and HC participants ($n = 2130$), examining $K = 9$ independent studies with an $N = 2714$. Finally, Wu et al. [12] informed about LDL-C, comparing $K = 33$ studies ($N = 8017$)

with n = 2843 AD and n = 5174 HC participants. Results indicated that the LDL-C serum levels were significantly higher in AD patients than in HC subjects. Heterogeneity was significant (Q = 9.05, df = 2; I^2 = 77.89%, p = 0.011, I^2 = 77.89%). (See Table 2).

Table 2. Summary effect sizes for low-density lipid cholesterol (LDL-C) serum levels and Alzheimer's disease (AD).

Model	Study	Statistics						
		OR	Lower Limit	Upper Limit	*Z*	*p*	Weight (Random)	Std Residual
	Zhou et al. [33]	1.89	1.24	2.86	2.98	0.003	40.64	−0.69
	Liu et al. [1]	12.67	3.56	45.08	3.92	0.000	18.96	2.13
	Wu et al. [12]	1.64	1.07	2.50	2.25	0.024	40.39	−1.01
Random effect		2.55	1.25	5.22	2.57	0.010		

3.2. Studies on HDL-C Levels

Three meta-analyses K = 3 (N = 23,642, n = 4147 AD and n = 19,495 HCs) showed a non-significant effect of HDL-C levels on the risk of AD: OR = 0.87, CI 95% [0.64, 1.18], Z = −0.89, p = 0.372, d = 0.08

Liu et al. [1] included 11 studies that analyzed HDL-C serum levels in AD patients and HCs. The combined sample size consisted of 2960 participants: 727 AD and 2233 HCs. They found non-significant differences between AD and HC subjects in HDL-C serum levels. Likewise, no differences were found between AD and HCs (K = 33 studies; N = 8192, n = 2921 AD and n = 5271 HCs) in the meta-analysis conducted by Wu et al. [12]. Finally, Xu et al. did not find any association between a lower level of HDL-C and AD (K = 6 studies; N = 12,490, n = 499 AD and n = 11,991 HCs). Heterogeneity was non-significant (Q = 3.85, df = 2; I^2 = 47.98%, p = 0.146). (See Table 3).

Table 3. Summary effect sizes for high-density lipid cholesterol (HDL-C) serum levels and AD.

Model	Study	Statistics						
		OR	Lower Limit	Upper Limit	*Z*	*p*	Weight (Random)	Std Residual
	Liu et al. [1]	0.38	0.13	1.13	−1.75	0.081	7.35	−1.46
	Wu et al. [12]	0.81	0.55	1.19	−1.07	0.285	33.30	−0.31
	Xu et al. [13]	1.00	0.87	1.16	0.00	1.000	59.35	1.08
Random effect		0.87	0.64	1.18	−0.89	0.374		

3.3. Studies on TC Levels

Results indicated that K = 4 meta-analyses (N = 2,271,785, n = 16,704 AD and n = 2,255,081 HCs) informed about the TC and AD risk. The combined effect size showed that TC levels increased by 44% the risk of AD, but this effect did not reach statistical significance: OR = 1.44 CI 95% [0.91, 2.28], Z = 1.55, p = 0.121, d = 0.20.

Liu et al. [1] included k = 13 primary studies (N = 3112) that compared the TC serum levels in AD (n = 809) and HC subjects (n = 2303), showing that TC levels were significantly higher in AD patients than in HC participants. Likewise, Wu et al. [12] reviewed K = 33 studies (N = 7850, n = 2661 AD patients and n = 5189 HCs), finding significant effects. However, Wang et al. [18] evaluated total of K= 16 studies (N = 1653), including 959 subjects with AD and 694 controls, finding non-significant differences between AD and HDs. In this study, the authors analyzed the markers of cholesterol in subjects with AD with age-matched controls. Finally, Xu et al. [13], in a longitudinal study, also reported non-significant differences between AD and HCs in TC levels (K = 16 studies; N = 2,259,170, n = 12,275 AD and n = 2,246,895 HCs). Heterogeneity was significant (Q = 11.83, df = 3; I^2 = 74.77%, p = 0.008). (See Table 4).

Table 4. Summary effect sizes for total cholesterol (TC) serum levels and Alzheimer's disease (AD).

Model	Study	Statistics						
		OR	Lower Limit	Upper Limit	*Z*	*p*	Weight (Random)	Std Residual
	Liu et al. [1]	3.97	1.25	12.55	2.35	0.019	11.41	1.55
	Wu et al. [12]	1.57	1.09	2.28	2.39	0.017	31.52	0.26
	Wang et al. [18]	1.52	0.70	3.25	1.07	0.283	19.04	0.11
	Xu et al. [13]	0.96	0.83	1.12	−0.4 −0.53	0.597	37.25	−1.35
Random effect		1.44	0.91	2.28	1.55	0.121		

3.4. Studies of TG Levels

The combined effect size of studies of TG levels $K = 2$ ($N = 8085$, $n = 2865$ AD and $n = 5220$ HCs), $OR = 1.22$, CI 95% [0.96, 1.56], $Z = 1.64$, $p = 0.102$, $d = 0.11$, indicates that there was no significant association between overall TG and the risk of AD. Liu et al. [1] ($K = 6$; $N = 512$, $n = 273$ AD, and $n = 239$ HCs) and Wu et al. [12] ($K = 28$; $N = 7573$, $n = 2592$ AD and $n = 4981$ HCs) showed that there were no differences in TG serum levels between patients and controls. Heterogeneity analysis was non-significant ($Q = 0.91$, $df = 1$; $I^2 = 0\%$, $p = 0.340$). (See Table 5).

Table 5. Summary effect sizes for triglycerides (TG) serum levels and Alzheimer's disease (AD).

Model	Study	Statistics						
		OR	Lower Limit	Upper Limit	*Z*	*p*	Weight (Random)	Std Residual
	Liu et al. [1]	1.04	0.68	1.57	0.17	0.864	33.61	−0.96
	Wu et al. [12]	1.33	0.99	1.79	1.89	0.059	66.39	0.96
Random effect		1.22	0.96	1.56	1.64	0. 102		

4. Discussion

This study analyzes the association between cholesterol levels and the risk of developing AD. This is the first attempt to evaluate this relation by identifying previous meta-analyses and their primary studies analyzed worldwide. The present meta-meta-analysis summarizes the information of 100 primary studies and expands the findings of individual studies.

Global results revealed that the level of cholesterol is a risk factor for AD. This finding is consistent with those from several prior studies, in which high cholesterol levels were associated with a higher likelihood of developing AD [1,4,12,13]. However, sensitivity analysis yielded several interesting and informative results. Even though the studies revealed that AD is involved in lipid metabolism, the results indicated that the effect of LDL-C, HDL-C, TC and TG on the development of dementia was different. We found that, compared with HC subjects, LDL-C levels were higher in AD participants, whereas HDL-C, TC and TG levels were not sensitive hallmarks of AD.

An elevated LDL cholesterol level was an independent risk factor for the development of AD. The pooled effect size exhibited a significant increase in the risk of AD for individuals with higher levels of LDL-C. Other prospective studies also support these results, showing that LDL concentration in mid-life increases the risk of developing AD in later life [34]. Nevertheless, in this study, the pathways through which elevated LDL cholesterol levels influence the development of dementia are unclear [35].

First, previous research indicated that the senile plaques theories may provide a link between high LDL-C and AD [36]. In this theory, elevated levels of LDL-C and TC cause the extracellular deposition of amyloid protein (Aβ), hindering neuronal synaptic connections in the brain and increasing the risk of AD [37].

Second, the Tau protein may play an important role in proper axonal transport and overall neural integrity [38] and correlates with cognitive decline in the AD. In this case, cognitive loss is associated with an excess of the Tau protein, which causes neurofibrillary tangles and prevents the synaptic connection of neurons in the brain [39].

In addition, risk factors for vascular disease may also be risk factors for AD, and high blood LDL-C levels are vascular risk factors [40]. Indeed, various studies have demonstrated that high concentrations of LDL cholesterol are associated with coronary heart disease and carotid artery atherosclerosis, which, in turn, may lead to cognitive decline through cerebral embolism or hypoperfusion [41–44]. The study conducted by Moroney et al. [45] also demonstrated that the level of LDL cholesterol is a potential risk factor for dementia with stroke. Therefore, it is necessary to analyze the influence of other factors related to LDL-C in the development of AD. This result could explain the heterogeneity between LDL-C studies found in this meta-meta-analysis.

The results showed no difference in HDL-C serum levels between AD and HC subjects. However, this result remains controversial, and no conclusive evidence was found. Various studies indicated that variations in HDL serum lipid levels are not associated with AD [1,12,13,35]. In other studies, lower levels of HDL have been associated with a high risk of AD [37,40]. Conversely, evidence suggests that high HDL-C levels are associated with a reduced risk of dementia, and that HDL may protect people against cerebrovascular dysfunction in AD [46]. In fact, cholesterol is an essential molecule for many physiologic processes and has multiple beneficial effects. Cholesterol is a precursor of steroid hormones (estrogens, androgens, vitamin D), it provides structural integrity and modulates the fluidity of cell membranes and is a main component of basic synaptic integrity and neurotransmission [47]. Moreover, HDL is known to have antioxidant and anti-inflammatory properties, which can affect neuroinflammatory responses in the brain and improve cognitive functions [48].

Whereas TC (total cholesterol) has been identified as a lipid marker for hyperlipemia [1,12,18], the summarized results did not find significant effects of TC levels on AD. Four meta-analyses assessing the effects of mid-life serum cholesterol on late-life risk of dementia and AD have yielded conflicting results. Several studies state that high cholesterol levels in middle age represent a risk factor for AD, but that there are no detectable differences in cholesterol levels at advanced ages [33,35,46]. Therefore, the non-significant effects of TC on AD in prospective studies (30 years to follow-up) could be explained by the variations in TC levels and the disease progression. Along these lines, Lepara et al. [44] indicated that cholesterol may be associated with AD cross-sectionally. In the same vein, Reitz [13] concluded that there is an association between higher cholesterol levels and a lower risk of AD, because of the nutritional status of elderly patients. In the early stages of AD, patients show alterations in the energy profile (weight loss, reduced caloric intake and increased energy requirements), and low cholesterol levels may reflect malnutrition [47]. Similarly, experimental studies and retrospective analyses in cohort studies indicate that statins could also affect the natural progress of the AD and reduce its prevalence over time [48]. Finally, even though Wang et al. [18] used a cross-sectional design, they did not find significant effects of TC on AD. In this study, the authors explained that cholesterol homeostasis could be altered in preclinical AD, whereas cholesterol dysregulation occurs throughout the disease's process. This evidence could make it more difficult to find a significant relationship between TC and AD during the disease's progress [18]. Hence, additional analysis is necessary.

The triglyceride serum level did not show a positive association with the development of AD in this meta-meta-analysis. This result also may be explained because of the retrospective design of some of the studies included herein. As we noted before, the use of cholesterol-lowering drugs could have suppressed the development of AD in participants, decreasing the likelihood of finding an association between TC and AD [49,50]. For instance, Wolozin [49] concluded that the use of statins, including lovastatin and pravastatin, decreased the development of AD. Other studies did not find that high triglyceride levels were associated with AD [1,12] and with potential changes in cognitive performance [51]. However, the results are not robust. Many studies associate hypercholesterolemia with the risk of dementia. Kivipelto [52] concluded that hypercholesterolemia could increase the risk of dementia, because arteriosclerosis occurs in the blood vessels, and this can alter blood flow, and directly induce neurodegeneration of AD [53]. Likewise, a recent study that investigated the association between diet and the level of triglycerides in the blood concluded that TG was associated with cognitive decline [54]. This result highlighted that a healthy diet and a good lifestyle for controlling

the serum lipid levels was beneficial for preventing AD, which seems to counteract the scientific literature, where TG level is not associated with AD [55].

Our summary results showed no statistically significant differences between serum HDL-C, TC and TG levels in patients with AD compared with HC participants. Based on all available information, this study reveals that it is important to identify early risk factors for AD, because the neurodegenerative processes of AD can begin at an early age, and pharmacological and non-pharmacological therapies that delay the neurodegenerative progress of AD may be performed. Moreover, it may be necessary for future studies to investigate in more detail the neural regions that exhibit different cholesterol content regarding the pathological processes related to AD [56], and the influence of other potential moderators that could explain the heterogeneity between the primary results. Hence, the relevance of our findings for the pathophysiology of AD needs to be further explored in future research.

The limitations of this study include the possibility of misclassification bias when using single baseline measurements of cholesterol and the lack of verification of the clinical diagnosis of dementia subtype. We were also unable to investigate the effect of other moderator variables, such as country or cohort. Perhaps the relationship between lipid levels and the risk of probable AD would change if the same cohort were analyzed. Moreover, we could not assess the possible association between dietary and exercise levels and LDL-C, HDL-C, TC and TG serum levels. In addition, other variables have been associated with AD, but the meta-analysis included lacked a description of these factors, so the results could not be further adjusted. Body mass index, smoking status, stroke, hypertension, Type 2 diabetes and heart disease are also closely related to blood lipid levels, and could affect the risk of AD.

However, this meta-meta-analysis represents a step toward evidence-based of AD and its relationship with dyslipidemia. First, this meta-meta-analysis provides an update and complete summary of the association of LDL-C, HDL-C, TC and TG with the prevalence of AD. Second, the effect sizes of one of the most studied risk factors for AD are provided to all healthcare professionals. Cholesterol is a modifiable risk factor, so if professionals know the relationship between cholesterol and AD, they could try to modify cholesterol levels to help to reduce AD risk. This study provides empirical evidence for the reduction of LDL-C levels through the promotion of healthy lifestyles (such as diet, weight control or physical activity) and/or the prescription of different medical treatments.

5. Conclusions

To sum up, the association of cholesterol and AD was evaluated. This meta-meta-analysis indicates that there is an association between the effect of cholesterol and AD. LDL-C, HDL-C, TC and TG were analyzed separately. LDL-C has a significant impact on the development of AD. Overall, this meta-meta-analysis represents a step toward evidence-based knowledge of AD.

The understanding of risk factors and protective factors of AD would require more long-term studies, conducting exhaustive follow-ups of each patient. Furthermore, this study highlighted the need to analyze other factors related to AD. Indeed, physical activity and the use of drugs could reduce the effects of cholesterol on AD; hence, more research is necessary. This meta-meta-analysis provides more knowledge about the relationship between cholesterol and AD, which could have a huge beneficial impact on AD incidence and prevalence.

Supplementary Materials: The following are available online at http://www.mdpi.com/2076-3425/10/6/386/s1. Table S1 showed the available primary studies of cholesterol and AD (K = 100 studies) and the main characteristics. It is worth noting that the search for suitable meta-analyses was systematic. To carry out the main analysis, cholesterol studies were divided into groups based on the type of lipid serum at which cholesterol was placed in each meta-analysis: LDL-C, HDL-C, TC, and TG. Table S2 illustrates the individual effect sizes obtained from the meta-analysis of the 100 primary studies to facilitate the replicability of this study and further analysis.

Author Contributions: Conceptualization, O.S., S.U., and J.P.; methodology, A.P.; formal analysis, A.P. and O.S.; investigation, O.S., J.P., and S.U.; data curation, A.P. and O.S..; writing—original draft preparation, A.P. and S.U.; writing—review and editing O.S., A.P. and S.U.; supervision, S.U., J.S. and J.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by a research grant from the Basque Country, Spain (awarded to A.P.), by the Junta of Castilla y León (Spain) to the Social Inclusion and Quality of Life (SIQoL) (No.665501), by FEDER funds and the Spanish Ministry of Economy and Competitiveness (Projects ECO2013-47129-C4-3-R and ECO2016-76567-C4-2-R), by the Regional Government of Castilla y León and FEDER funds (Projects BU329U14, BU071G19 and BU062U16), and by the Fondo de Investigación Sanitaria, Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness, Madrid, Spain (grants 94/1562, 97/1321E, 98/0103, 01/0255, 03/0815, 06/0617, G03/128, 19/01874).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Liu, Y.; Zhong, X.; Shen, J.; Jiao, L.; Tong, J.; Zhao, W.; Du, K.; Gong, S.; Liu, M.; Wei, M. Elevated serum TC and LDL-C levels in Alzheimer's disease and mild cognitive impairment: A meta-analysis study. *Brain Res.* **2020**, *1727*, 146554. [CrossRef] [PubMed]
2. Martin, P.; Anders, W.; Maëlenn, G.; Ali, G.C.; Wu, Y.-T.; Prina, M. *World Alzheimer Report 2015: The Global Impact of Dementia*; Alzheimer's Disease International (ADI): London, UK, 2015.
3. Kapogiannis, D.; Mustapic, M.; Shardell, M.D.; Berkowitz, S.T.; Diehl, T.C.; Spangler, R.D.; Tran, J.; Lazaropoulos, M.P.; Chawla, S.; Gulyani, S. Association of extracellular vesicle biomarkers with Alzheimer disease in the Baltimore longitudinal study of aging. *JAMA Neurol.* **2019**, *76*, 1340–1351. [CrossRef] [PubMed]
4. Wang, C.; Shou, Y.; Pan, J.; Du, Y.; Liu, C.; Wang, H. The relationship between cholesterol level and Alzheimer's disease-associated APP proteolysis/Aβ metabolism. *Nutr. Neurosci.* **2019**, *22*, 453–463. [CrossRef] [PubMed]
5. Khachaturian, Z.S.; Khachaturian, A.S. Politics of science: Progress toward prevention of the dementia–Alzheimer's syndrome. *Mol. Aspects Med.* **2015**, *43*, 3–15. [CrossRef] [PubMed]
6. Niu, H.; Álvarez-Álvarez, I.; Guillén-Grima, F.; Aguinaga-Ontoso, I. Prevalencia e incidencia de la enfermedad de Alzheimer en Europa: Metaanálisis. *Neurología* **2017**, *32*, 523–532. [CrossRef]
7. Cao, Q.; Tan, C.-C.; Xu, W.; Hu, H.; Cao, X.-P.; Dong, Q.; Tan, L.; Yu, J.T. The Prevalence of Dementia: A Systematic Review and Meta-Analysis. *J. Alzheimers Dis.* **2020**, *73*, 1157–1166. [CrossRef]
8. Pedro-Cuesta, J.; Virués-Ortega, J.; Vega, S.; Seijo-Martínez, M.; Saz, P.; Rodríguez, F.; Rodríguez-Laso, A.; Reñé, R.; de las Heras, S.P.; Mateos, R.; et al. Prevalence of dementia and major dementia subtypes in Spanish populations: A reanalysis of dementia prevalence surveys, 1990–2008. *BMC Neurol.* **2009**, *9*, 55. [CrossRef]
9. Dement, A. Alzheimer's disease facts and figures. *Alzheimer's Dement. J. Alzheimer's Assoc.* **2016**, *12*, 459–509. [CrossRef]
10. Lesser, G.T. Association of Alzheimer Disease Pathology with Abnormal Lipid Metabolism: The Hisayama Study. *Neurology* **2012**, *78*, 1280. [CrossRef]
11. Agirbasli, M.; Tanrikulu, A.; Sevim, B.A.; Azizy, M.; Bekiroglu, N. Total cholesterol-to-high-density lipoprotein cholesterol ratio predicts high-sensitivity C-reactive protein levels in Turkish children. *J. Clin. Lipidol.* **2015**, *9*, 195–200. [CrossRef]
12. Wu, Y.; Wang, Z.; Jia, X.; Zhang, H.; Zhang, H.; Li, J.; Zhang, K. Prediction of Alzheimer's disease with serum lipid levels in Asian individuals: A meta-analysis. *Biomarkers* **2019**, *24*, 341–351. [CrossRef] [PubMed]
13. Xu, W.; Tan, L.; Wang, H.-F.; Jiang, T.; Tan, M.-S.; Tan, L.; Zhao, Q.-F.; Li, J.-Q.; Wang, J.; Yu, J.-T. Meta-analysis of modifiable risk factors for Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **2015**, *86*, 1299–1306. [CrossRef] [PubMed]
14. Whitmer, R.A.; Sidney, S.; Selby, J.; Johnston, S.C.; Yaffe, K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* **2005**, *64*, 277–281. [CrossRef] [PubMed]
15. Versmissen, J.; Oosterveer, D.M.; Hoekstra, M.; Out, R.; Berbée, J.F.; Blommesteijn-Touw, A.C.; van Vark-van der Zee, L.; Vongpromek, R.; Vanmierlo, T.; Defesche, J.C.; et al. Apolipoprotein Isoform E4 Does Not Increase Coronary Heart Disease Risk in Carriers of Low-Density Lipoprotein Receptor Mutations. *Circ. Cardiovasc. Genet.* **2011**, *4*, 655–660. [CrossRef] [PubMed]
16. Nägga, K.; Gustavsson, A.-M.; Stomrud, E.; Lindqvist, D.; van Westen, D.; Blennow, K.; Zetterberg, H.; Melander, O.; Hansson, O. Increased midlife triglycerides predict brain β-amyloid and tau pathology 20 years later. *Neurology* **2018**, *90*, e73–e81. [CrossRef] [PubMed]
17. Hardy, J. Alzheimer's disease: The amyloid cascade hypothesis: An update and reappraisal. *J. Alzheimers Dis.* **2006**, *9*, 151–153. [CrossRef]

18. Wang, H.-L.; Wang, Y.-Y.; Liu, X.-G.; Kuo, S.-H.; Liu, N.; Song, Q.-Y.; Wang, M.-W. Cholesterol, 24-Hydroxy cholesterol, and 27-Hydroxycholesterol as Surrogate Biomarkers in Cerebrospinal Fluid in Mild Cognitive Impairment and Alzheimer's Disease: A Meta-Analysis. *J. Alzheimers Dis.* **2016**, *51*, 45–55. [CrossRef]
19. Shibata, N.; Ohnuma, T.; Higashi, S.; Higashi, M.; Usui, C.; Ohkubo, T.; Watanabe, T.; Kawashima, R.; Kitajima, A.; Ueki, A.; et al. No genetic association between PCSK9 polymorphisms and Alzheimer's disease and plasma cholesterol level in Japanese patients. *Psychiatr. Genet.* **2005**, *15*, 239. [CrossRef]
20. Tynkkynen, J.; Hernesniemi, J.A.; Laatikainen, T.; Havulinna, A.S.; Sundvall, J.; Leiviskä, J.; Salo, P.; Salomaa, V. Apolipoproteins and HDL cholesterol do not associate with the risk of future dementia and Alzheimer's disease: The National Finnish population study (FINRISK). *AGE* **2016**, *38*, 465–473. [CrossRef]
21. Michikawa, M. Cholesterol paradox: Is high total or low HDL cholesterol level a risk for Alzheimer's disease? *J. Neurosci. Res.* **2003**, *72*, 141–146. [CrossRef]
22. Wolf, H.; Hensel, A.; Arendt, T.; Kivipelto, M.; Winblad, B.; Gertz, H.J. Association between serum HDL cholesterol and hippocampal volume: A link to Alzheimer's disease? *Neurobiol. Aging* **2004**, *25*, 52. [CrossRef]
23. Moher, D. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann. Intern. Med.* **2009**, *151*, 264. [CrossRef] [PubMed]
24. Shea, B.J.; Grimshaw, J.M.; Wells, G.A.; Boers, M.; Andersson, N.; Hamel, C.; Porter, A.C.; Tugwell, P.; Moher, D.; Bouter, L.M. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. *BMC Med. Res. Methodol.* **2007**, *7*, 10. [CrossRef] [PubMed]
25. Shea, B.J.; Hamel, C.; Wells, G.A.; Bouter, L.M.; Kristjansson, E.; Grimshaw, J.; Henry, D.A.; Boers, M. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J. Clin. Epidemiol.* **2009**, *62*, 1013–1020. [CrossRef] [PubMed]
26. Cleophas, T.J.; Zwinderman, A.H. Meta-Meta-analysis. In *Modern Meta-Analysis. Review and Update of Methodologies*; Springer: Berlin/Heidelberg, Germany, 2017; pp. 135–143. [CrossRef]
27. Reis, H.T.; Judd, C.M. *Handbook of Research Methods in Social and Personality Psychology*; Cambridge University Press: Cambridge, UK, 2000.
28. Shrier, I.; Steele, R. Understanding the Relationship between Risks and Odds Ratios. *Clin. J. Sport Med.* **2006**, *16*, 107–110. [CrossRef] [PubMed]
29. Singh, A.; Hussain, S.; Najmi, A.K. Number of studies, heterogeneity, generalisability, and the choice of method for meta-analysis. *J. Neurol. Sci.* **2017**, *381*, 347. [CrossRef]
30. Borenstein, M.; Hedges, L.V.; Higgins, J.P.; Rothstein, H.R. *Introduction to Meta-Analysis*; John Wiley & Sons: Hoboken, NJ, USA, 2011.
31. Borenstein, M.; Hedges, L.; Higgins, J.P.T.; Rothstein, H. *Comprehensive meta-analysis version 3*, Biostat: Englewood, NJ, USA, 2013.
32. Cohen, J. *Statistical Power Analysis For The Behavioral Sciences*; Academic Press: Cambridge, MA, USA, 2013. [CrossRef]
33. Zhou, Z.; Liang, Y.; Zhang, X.; Xu, J.; Lin, J.; Zhang, R.; Kang, K.; Liu, C.; Zhao, C.; Zhao, M. Low-Density Lipoprotein Cholesterol and Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Front. Aging Neurosci.* **2020**, *12*, 5. [CrossRef]
34. Hall, J.R.; Wiechmann, A.R.; Johnson, L.A.; Edwards, M.; Barber, R.C.; Cunningham, R.; Singh, M.; O'bryant, S.E. Total cholesterol and neuropsychiatric symptoms in Alzheimer's disease: The impact of total cholesterol level and gender. *Dement. Geriatr. Cogn. Disord.* **2014**, *38*, 300–309. [CrossRef]
35. Tan, Z.S.; Seshadri, S.; Beiser, A.; Wilson, P.W.; Kiel, D.P.; Tocco, M.; D'Agostino, R.B.; Wolf, P.A. Plasma total cholesterol level as a risk factor for Alzheimer disease: The Framingham Study. *Arch. Intern. Med.* **2003**, *163*, 1053–1057. [CrossRef]
36. Launer, L.J.; White, L.R.; Petrovitch, H.; Ross, G.W.; Curb, J.D. Cholesterol and neuropathologic markers of AD: A population-based autopsy study. *Neurology* **2001**, *57*, 1447–1452. [CrossRef]
37. Reitz, C.; Tang, M.-X.; Luchsinger, J.; Mayeux, R. Relation of plasma lipids to Alzheimer disease and vascular dementia. *Arch. Neurol.* **2004**, *61*, 705–714. [CrossRef] [PubMed]
38. Lauretti, E.; Praticò, D. Alzheimer's disease: Phenotypic approaches using disease models and the targeting of tau protein. *Expert Opin. Ther. Targets* **2020**. [CrossRef] [PubMed]
39. Theofilas, P.; Ehrenberg, A.J.; Nguy, A.; Thackrey, J.M.; Dunlop, S.; Mejia, M.B.; Alho, A.T.; Leite, R.E.P.; Rodriguez, R.D.; Suemoto, C.K. Probing the correlation of neuronal loss, neurofibrillary tangles, and cell

death markers across the Alzheimer's disease Braak stages: A quantitative study in humans. *Neurobiol. Aging* **2018**, *61*, 1–12. [CrossRef] [PubMed]
40. Carleton, R.A.; Dwyer, J.; Finberg, L.; Flora, J.; Goodman, D.S.; Grundy, S.M.; Havas, S.; Hunter, G.T.; Kritchevsky, D.; Lauer, R.M. Report of the Expert Panel on Population Strategies for Blood Cholesterol Reduction. A statement from the National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health. *Circulation* **1991**, *83*, 2154–2232. [CrossRef]
41. Sharrett, A.R.; Patsch, W.; Sorlie, P.D.; Heiss, G.; Bond, M.G.; Davis, C.E. Associations of lipoprotein cholesterols, apolipoproteins AI and B, and triglycerides with carotid atherosclerosis and coronary heart disease. The Atherosclerosis Risk in Communities (ARIC) Study. *Arterioscler. Thromb. J. Vasc. Biol.* **1994**, *14*, 1098–1104. [CrossRef]
42. Breteler, M.M.; Claus, J.J.; Grobbee, D.E.; Hofman, A. Cardiovascular disease and distribution of cognitive function in elderly people: The Rotterdam Study. *BMJ* **1994**, *308*, 1604–1608. [CrossRef]
43. Tatemichi, T.K.; Desmond, D.W.; Prohovnik, I.; Eidelberg, D. Dementia associated with bilateral carotid occlusions: Neuropsychological and haemodynamic course after extracranial to intracranial bypass surgery. *J. Neurol. Neurosurg. Psychiatry* **1995**, *58*, 633–636. [CrossRef]
44. Moroney, J.T.; Tang, M.-X.; Berglund, L.; Small, S.; Merchant, C.; Bell, K.; Stern, Y.; Mayeux, R. Low-density lipoprotein cholesterol and the risk of dementia with stroke. *JAMA* **1999**, *282*, 254–260. [CrossRef]
45. Dias, I.H.; Polidori, M.C.; Li, L.; Weber, D.; Stahl, W.; Nelles, G.; Grune, T.; Griffiths, H.R. Plasma levels of HDL and carotenoids are lower in dementia patients with vascular comorbidities. *J. Alzheimers Dis.* **2014**, *40*, 399–408. [CrossRef]
46. Button, E.B.; Robert, J.; Caffrey, T.M.; Fan, J.; Zhao, W.; Wellington, C.L. HDL from an Alzheimer's disease perspective. *Curr. Opin. Lipidol.* **2019**, *30*, 224. [CrossRef]
47. Lepara, O.; Valjevac, A.; Alajbegović, A.; Zaćiragić, A.; Nakaš-Ićindić, E. Decreased serum lipids in patients with probable Alzheimer's disease. *Bosn. J. Basic Med. Sci.* **2009**, *9*, 215. [CrossRef] [PubMed]
48. Reitz, C.; Tang, M.-X.; Schupf, N.; Manly, J.J.; Mayeux, R.; Luchsinger, J.A. Association of higher levels of high-density lipoprotein cholesterol in elderly individuals and lower risk of late-onset Alzheimer disease. *Arch. Neurol.* **2010**, *67*, 1491–1497. [CrossRef] [PubMed]
49. Wolozin, B.; Kellman, W.; Ruosseau, P.; Celesia, G.G.; Siegel, G. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. *Arch. Neurol.* **2000**, *57*, 1439–1443. [CrossRef] [PubMed]
50. Jick, H.; Zornberg, G.L.; Jick, S.S.; Seshadri, S.; Drachman, D.A. Statins and the risk of dementia. *Lancet* **2000**, *356*, 1627–1631. [CrossRef]
51. Reitz, C.; Luchsinger, J.; Tang, M.-X.; Manly, J.; Mayeux, R. Impact of plasma lipids and time on memory performance in healthy elderly without dementia. *Neurology* **2005**, *64*, 1378–1383. [CrossRef] [PubMed]
52. Kivipelto, M.; Helkala, E.-L.; Laakso, M.P.; Hänninen, T.; Hallikainen, M.; Alhainen, K.; Soininen, H.; Tuomilehto, J.; Nissinen, A. Midlife vascular risk factors and Alzheimer's disease in later life: Longitudinal, population based study. *BMJ* **2001**, *322*, 1447–1451. [CrossRef]
53. Skoog, I.; Kalaria, R.N.; Breteler, M.M. Vascular factors and Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* **1999**, *13*, S106–s114. [CrossRef]
54. An, Y.; Zhang, X.; Wang, Y.; Wang, Y.; Liu, W.; Wang, T.; Qin, Z.; Xiao, R. Longitudinal and nonlinear relations of dietary and Serum cholesterol in midlife with cognitive decline: Results from EMCOA study. *Mol. Neurodegener.* **2019**, *14*, 1–19. [CrossRef]
55. Clark, L.R.; Norton, D.; Berman, S.E.; Johnson, S.C.; Bendlin, B.B.; Wieben, O.; Turski, P.; Carlsson, C.; Asthana, S.; Gleason, C.E. Association of Cardiovascular and Alzheimer's Disease Risk Factors with Intracranial Arterial Blood Flow in Whites and African Americans. *J. Alzheimers Dis.* **2019**, 1–11. [CrossRef]
56. Yanagisawa, K. Cholesterol and pathological processes in Alzheimer's disease. *J. Neurosci. Res.* **2002**, *70*, 361–366. [CrossRef]

Journal of
Clinical Medicine

MDPI

Review

Depression as a Risk Factor for Alzheimer's Disease: A Systematic Review of Longitudinal Meta-Analyses

Olalla Sáiz-Vázquez [1], Patricia Gracia-García [2], Silvia Ubillos-Landa [3,*], Alicia Puente-Martínez [4], Silvia Casado-Yusta [5], Beatriz Olaya [6,7] and Javier Santabárbara [7,8,9]

1 Department of Occupational Therapy, Faculty of Health Science, University of Burgos, C/Paseo de los Comendadores, Hospital Militar, 1, 09001 Burgos, Spain; osaiz@ubu.es
2 Psychiatry Service, Hospital Universitario Miguel Servet, 50009 Zaragoza, Spain; pgraciag@salud.aragon.es
3 Department of Social Psychology, Faculty of Health Science, University of Burgos, C/Villadiego, 1, 09001 Burgos, Spain
4 Department of Social Psychology, Faculty of Health Science, University of Burgos, C/Paseo de los Comendadores, Hospital Militar, 1, 09001 Burgos, Spain; alicia.puente@ehu.es
5 Department of Applied Economy, Faculty of Economics and Business Sciences, University of Burgos, Pza. De la Infanta Dª Elena, 09001 Burgos, Spain; scasado@ubu.es
6 Research, Innovation and Teaching Unit, Parc Sanitari Sant Joan de Déu, Universitat de Barcelona, Carrer Doctor Pujadas 42, 08830 Sant Boi de Llobregat, Spain; beatriz.olaya@pssjd.org
7 Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Ministry of Science and Innovation, Av. Monforte de Lemos 3-5, Pabellón 11, Planta 0, 28029 Madrid, Spain; jsantabarbara@unizar.es
8 Department of Microbiology, Pediatrics, Radiology and Public Health, University of Zaragoza, C/Domingo Miral s/n, 50009 Zaragoza, Spain
9 Aragonese Institute of Health Sciences (IIS Aragón), 50009 Zaragoza, Spain
* Correspondence: subillos@ubu.es; Tel.: +34-947-258-074

Citation: Sáiz-Vázquez, O.; Gracia-García, P.; Ubillos-Landa, S.; Puente-Martínez, A.; Casado-Yusta, S.; Olaya, B.; Santabárbara, J. Depression as a Risk Factor for Alzheimer's Disease: A Systematic Review of Longitudinal Meta-Analyses. *J. Clin. Med.* **2021**, *10*, 1809. https://doi.org/10.3390/jcm10091809

Academic Editor: Marco Bozzali

Received: 10 March 2021
Accepted: 15 April 2021
Published: 21 April 2021

Abstract: Alzheimer's disease (AD) is the most frequent cause of dementia, linked to morbidity and mortality among elderly patients. Recently, several clinical studies suggested that depression is a potential risk factor for cognitive decline and AD. A review of meta-analyses was performed, calculating pooled odds ratios to estimate the risk of AD in people with a prior diagnosis (or clinically significant symptoms) of depression. A total of six meta-analyses which represented 28 individual studies were analyzed. A significant association between depression and AD was found (OR = 1.54, 95% CI [1.02–2.31]; $p = 0.038$). The results showed that heterogeneity across studies was substantial. We found a significant positive effect size for clinical measures of depression, but not for symptomatic rating scales, in the association of depression with risk of AD. The type of rating scale used to assess depression and the cut-off criteria selected also moderated the relationship between depression and AD risk. We found that studies that used clinically significant criteria for diagnosis of depression had more consistent and significant results than studies that used symptomatic scales.

Keywords: depression; Alzheimer's disease; clinical and symptomatic criteria; meta-meta-analysis

1. Introduction

Alzheimer's disease (AD) is the most frequent cause of dementia and is considered one of the main causes of morbidity and mortality among elderly people [1]. The World Alzheimer's Report revealed that 46.8 million people worldwide were living with dementia in 2015, and the total global social cost of dementia was estimated to be $818 billion [2]. Estimates of dementia incidence in population-based studies range from 5 to 10 cases per 1000 person-years in people aged 64 to 69, and up to 40 to 60 cases per 1000 person-years in people aged 80 to 84 [3]. In 2017 in Europe, prevalence rates of AD were reported to be 5.05%, with 3.31% in men and 7.13% in women [4]. Given the personal and social consequences of dementia and AD demand, we accelerate the global effort to understand this complex disorder [5].

Decades of research revealed that the pathophysiological mechanisms underlying this neurodegenerative disease include accumulation of amyloid-beta peptide (Aβ) in brain tissues and cytoskeletal changes related to the hyperphosphorylation of microtubule-associated Tau protein in neurons. As a consequence, neuritic plaques and neurofibrillary tangles are accumulated, mostly in the medial temporal lobe and associative neocortical areas [6], and resulting in several cognitive deficits. The clinical manifestation of AD is progressive, from unnoticeable brain changes to brain changes that cause cognitive deterioration and eventually physical disability [7]. AD usually begins with memory difficulties followed by other cognitive problems such as visuospatial abnormalities, navigation difficulties, executive problems, and language disturbance [2].

Evidence seems to suggest that the etiology of AD is multifactorial, with genetics, older age, and a family history of AD being the greatest contributors to a higher risk of AD [7]. Furthermore, AD is often associated with other chronic diseases (diabetes, cholesterol, cardiovascular diseases, obesity, and hypertension) [8]. Although these risk factors are unchangeable, other risk factors can be modified to reduce the risk of dementia and cognitive decline. This is particularly important, since there is no currently available way to stop the damage and destruction of neurons linked to AD.

Depressive symptoms are common in AD and occur in approximately 20–30% of patients [9]. Depression is a serious medical illness that affects about 300 million people worldwide and which might aggravate existing medical conditions and increase functional disability [9,10]. Clinical evidence suggests a relationship between depression and AD [11–14]. However, it remains unclear whether depression represents a risk factor for AD, is an early symptom of neurodegeneration, or is a reaction to early cognitive deficits [14,15]. Some studies have suggested that depressive symptoms immediately follow the onset of AD rather than precede it [16]. Moreover, evidence from other studies indicates that depression has only a mild effect on dementia [17] and does not increase the risk for developing AD [18]. However, other authors suggest that the presence of depression in patients with AD increases the risk of behavioral disturbance and accelerates functional decline [12]. Hudon et al. [19], for example, found that depression was the most consistent risk factor associated with behavioral or psychological symptoms and cognitive decline in patients with AD. In addition, several studies concluded that late-life depression is related to an increased risk for all-cause dementia, vascular dementia, and Alzheimer's disease [20–22], and late-life depression was shown to be associated consistently with a two-fold increased risk of dementia [23,24].

In order to clarify the role of depression as a risk factor of AD, several meta-analyses were conducted [19,20,22,23]. However, some limitations were pointed out. Cherbuin et al. [24], for example, indicated that, in general, results from previous studies that focused on depression as a risk factor of AD might be biased due to the type of instrument used to assess depression. Results are frequently based on different tools. Some of these studies are based on symptomatic rating scales with cut-off points (e.g., CESD), while others are based on clinical criteria (e.g., DSM). Thus, the pooled estimates of the risk for AD in depressed people might be unreliable, because these meta-analyses combined effect sizes from studies using different instruments to assess depression (i.e., symptomatic rating scales and clinical diagnoses). Additionally, these previous meta-analyses did not pool findings separately for studies using clinical criteria and studies using depressive symptom rating scales with specified cut-off points.

Based on these limitations and the inconclusive evidence, we aimed to perform a meta-meta-analysis of longitudinal studies to assess the effect of depression on the risk of a subsequent diagnosis of AD. Given the expected heterogeneity among studies, we also aimed to pool findings separately from studies using clinical criteria and those using depression symptom rating scales, and to test the association between depression and risk of AD according to the different instruments used.

2. Materials and Methods

2.1. Data Collection

This meta-meta-analysis was performed in accordance with the Preferred Reporting for Systematic Reviews and Meta-analysis (PRISMA) Statement [25]. For data collection, we searched meta-analyses that measured depression at baseline and reported outcomes in individuals with diagnoses of AD at follow-up. ISI Web of Science (WOS), Scopus, Pubmed, Elsevier Science Direct, and Google scholar were searched from inception up to 31 July 2020. Combinations of the following search terms were used: "depression" AND "Alzheimer's disease" AND "meta-analysis". The data search was done in English (four studies) and Spanish (one study). When necessary, corresponding authors were contacted to provide full text details of the study outcome measures.

2.2. Inclusion Criteria

By consensus of the authors, studies were included if they met the following criteria:

1. Longitudinal studies that investigated the effect of depression or depressive symptoms (at baseline) as an antecedent to AD (follow-up).
2. Studies including patients with a diagnosis of AD according to diagnosis criteria (e.g., Related Disorders Association criteria, N-ADRDA, the Diagnostic and Statistical Manual of mental Disorders, DSM-III or the National Institute of Neurological and Communication Disorders-Alzheimer's Disease).
3. Studies that clinically assessed levels of depression by means of a clinical diagnosis (e.g., DSM-IV, ICD-10), or a symptomatic diagnostic tool with a cut-off score (e.g., Geriatric Mental State Schedule, GMS) that identifies clinically significant levels of depression.
4. Studies reporting sufficient information to calculate common effect size statistics (i.e., mean and SD, exact P-, t-, or z-values).
5. Original, peer-reviewed meta-analyses that were published in English and Spanish.

2.3. Exclusion Criteria

By consensus of the authors, the following were excluded:

1. Studies investigating the association of depression and risk of AD using a sample of patients with AD and other dementia (non-independent or overlapping data for AD).
2. Studies not reporting quantitative data to calculate the association between depression and AD, or not published as meta-analyses in peer-reviewed journals (i.e., conference abstracts, book chapters).
3. Meta-analyses about other topics or those that included the same primary studies.

2.4. Data Extraction and Quality Assessment

Titles and abstracts of potential meta-analyses about depression and incident AD were independently analyzed by three researchers (OS, SU, PG). After exclusion of irrelevant articles, the remaining meta-analyses were critically inspected to check data accuracy. Then, full texts of all primary studies included in each meta-analysis were screened according to the inclusion criteria. In the event of ambiguity, two authors (SU, JS) additionally reviewed the study to reach a consensus regarding its eligibility.

Data related to the diagnosis/assessment of depression and AD were collected directly from the text or from statistical tables. The lead author and either the third or fourth author independently extracted data from each study, including study characteristics (year, country, total sample size, and length of follow-up period), sample characteristics (mean age, % of women), measures of depression and AD, and the cut-off point used for depression in each individual study.

Diagnoses of AD were based on the following accepted clinical criteria: Revised criteria and the National Institute of Neurological and Communication Disorders-Alzheimer's Disease and Related Disorders Association criteria (N-ADRDA), the Diagnostic and Sta-

tistical Manual of Mental Disorders in different editions (DSM-III, DSM-III-R, DSM-IV, DSM-V), and the International Classification of diseases (ICD-10). Additionally, studies established different cut-off scores on neuropsychological tests for the purposes of screening out cognitive impairment and dementia at baseline (see Table 1). Participants with scores above the cut-off on cognitive domains were excluded on the basis that this level of test performance indicates the presence of dementia or cognitive impairment. The most frequently used measures to describe the cognitive characterization of the participants at baseline were the Mini Mental State Examination (MMSE) (n = 14) and the Clinical Rating Scale (CRS) (n = 6). Diagnoses of depression were based on either symptomatic rating scales or clinical diagnoses. Clinical criteria for depression included the DSM-III, DSM-III-R, DSM-IV, DSM-V, and the Automated Geriatric Examination for Computer Assisted Taxonomy (GMS-AGECAT). Diagnoses of depression were based on symptomatic rating scales on valid cut-off points (SGDS/15/30, CES-D/10/11/20, HRSD-17).

In addition, the quality of the included studies was reported using the Assessment of Multiple Systematic Reviews (AMSTAR) tool [26], which was previously shown to have good inter-rater agreement, reliability, and content validity [26,27].

2.5. Statistical Analysis

Crude odds ratios (ORs) (and 95% confidence intervals (CIs)) were used to calculate the risk of developing AD associated with previous depression. When the number of cases of depression and AD were not provided, the effect sizes were calculated using reported data in the meta-analysis according to Lipsey and Wilson [28]. We considered HRs and ORs as equivalent, since it was previously shown that for rare events, they can be considered equivalent (incidence < 15%) [29]. Seventeen studies provided data that could be used in calculating crude ORs (odds of an outcome in the intervention arm divided by the odds of an outcome in the control). Eleven additional studies provided data on AD risk in samples as HR or ORs with 95% confidence intervals that could be used in pooling estimates.

Summary statistics were calculated using Comprehensive Meta-Analysis software (CMA; Version 3) (Biostat Inc., Englewood, NJ, USA) [30,31]. Initially, we performed an analysis summarizing all data available, including all studies with validated cut-offs or clinical diagnoses in a single pooled estimate [31]. For each study, we calculated: (a) 95% CI of the effect, (b) Z value and p (two-tailed significance), and (c) k or number of studies [32]. Presence of publication bias was assessed through visual inspection of funnel plots and with Egger's test [16].

The level of heterogeneity was assessed with the I2 statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance alone. An I2 value of 25% indicates low heterogeneity, 50% moderate heterogeneity, and 75% high heterogeneity [31]. Random-effect models were used to determine statistically significant heterogeneity. Additionally, the Cochran Q test was applied to assess significant heterogeneity (p-value < 0.05). Moderating variables were selected on the basis of substantive considerations and the availability of data across studies included in the meta-analysis. Subgroup analyses were performed according to how depression was assessed: by clinical diagnosis (e.g., DSM-V) or by symptomatic rating scales (e.g., CES-D). Additionally, because the studies included different symptomatic rating scales, we also considered the instrument and the specific cut-off criteria as moderating variables. Therefore, we calculated the effect sizes of the association between depression and risk of AD separately for studies using different cut-off points. Finally, meta-regression analyses were conducted to obtain the proportion of variance explained for each moderator (the R-square analog). The scatter plot represents the mean effect for each level of covariate.

Table 1. Summary of demographic and study information.

Study	Year	Country	AD Measure [1]	Cognitive Measure [2]	Cut-Off Criteria Cognition	Depression Measure [3]	Cut-Off Criteria Depression [4]	*n* [5]	Follow-Up Length (Years) *M* (*SD*)	Age *M* (*SD*)	Female (%) (Total)	AMSTAR2 [6]
Bae et al. [33]	2015	AS	N-ADRDA	CERAD-K	≥60	GDS15	≥8	540	3.5 (0.3)	71.7 (5.1)	55.2	HIGH
Bartolini et al. [34]	2005	EU	N-ADRDA	MMSE	>26	DSM-III-R	-	222	1	69.2 (4.8)	63.5	HIGH
Becker et al. [18]	2009	USA	N-ADRDA	MMSE	>26	CES-D20	≥10	729	7.1 (NR)	70	69	HIGH
Blasko et al. [35]	2010	Austria	N-ADRDA	CERAD	≥60	DSM-IV	-	648	2.5 (NR)	78.3 (0.5)	56.5	HIGH
Burke et al. [36]	2018	USA	N-ADRDA	CRS	≤3	DSM-V	-	12,083	4.2 (-)	63.9	83	HIGH
Chen et al. [37]	1999	USA	DSM-III-R	MMSE	>26	CES-D20	≥16	803	4.5 (NR)	73.7 (5.0)	60	MODERATE
Dal Forno et al. [38]	2005	USA	N-ADRDA	BIMC		CES-D20	≥20	1357	6.1 (-)	65.5 (12.0)	45.5	HIGH
Devanand et al. [39]	1996	USA	N-ADRDA	CRS	≤3	DSM-III R	-	456	2.54	72	70	HIGH
Dotson, Beydoun & Zonderman [40]	2010	USA	DSM-III R	BIMC		CES-D20	≥16	2177	23.6 (NR)	52.7 (18.8)	42.3	HIGH
Fuhrer, Dufouil & Dartigues [41]	2003	France	N-ADRDA/DSM-III-R	MMSE	>26	CES-D20	≥16	1576	8.0 (NR)	75.2 (6.9)	58.3	HIGH
Gatz et al. [16]	2005	Canada	DSM-III R	MMSE	>26	CES-D20	≥16	766	5	74.5 (6.0)	61.7	HIGH
Geerlings et al. [42]	2000	Países Bajos	DSM-III-R	MMSE	>26	GMS-AGECAT	-	1911	5,9 (1,6)	73.5 (7.9)	49	MODERATE
Geerlings et al. [43]	2008	Netherlands	N-ADRDA	MMSE	>26	CES-D20	≥16	393	5.9 (1.6)	73.5 (7.9)	49	MODERATE
Gracia-García et al. [44]	2015	EU	DSM-IV	MMSE	>26	GMS-AGECAT	≥3	3626	4.5	71.9 (9.0)	54.4	HIGH
Heser et al. [45]	2013	Germany	DSM-IV/ICD-10	MMSE	>26	DSM-IV	-	2969	4	81	64.8	HIGH
Irie et al. [46]	2008	USA	N-ADRDA	CRS	≤3	CES-D11	≥9	1585	5.1	76.3 (3.6)	0	HIGH
Kim et al. [47]	2010	South Korea	N-ADRDA	CRS	≤3	GDS30	13/14	473	2.4 (0.3)	71.8 (5.1)	54.4	HIGH
Kim et al. [48]	2011	South Korea	DSM-IV	CRS	≤3	GMS-AGECAT	≥3	563	2.4 (0.3)	71.8 (5.0)	54.4	MODERATE
Lauriola et al. [49]	2018	EU	DSM-V	MMSE	>26	DSM-V	-	181	4	74.5 (7.5)	59.7	HIGH
Lenoir et al. [50]	2011	France	N-ADRDA	MMSE	>26	CES-D20	M ≥ 16 W ≥ 22	7989	4 (NR)	74.0 (5.4)	61.3	HIGH
Li et al. [51]	2011	USA	N-ADRDA	CASI	≥78	CES-D11	≥10/	3410	7.1 (NR)	74.9 (6.2)	59.9	HIGH
Luchsinger et al. [52]	2008	USA	N-ADRDA	CRS	≤3	HRSD17	≥10	1138	5.1 (3.3)	75.1 (6.4)	67.7	HIGH
Reding, Haycox & Blass [53]	1985	USA	ICD-10	MSQ	0–2 errors	DSM-III	-	60	3	-	-	MODERATE
Richard et al. [54]	2013	USA	DSM-III R	MMSE	>26	CES-D10	≥4	2160	-	76.9 (7.1)	75	MODERATE
Saczynski et al. [55]	2010	USA	N-ADRDA	MMSE	>26	CES-D20	≥16	949	8 (NR)	79.3 (5.0)	63.6	MODERATE

Table 1. *Cont.*

Study	Year	Country	AD Measure [1]	Cognitive Measure [2]	Cut-Off Criteria Cognition	Depression Measure [3]	Cut-Off Criteria Depression [4]	*n* [5]	Follow-Up Length (Years) *M* (*SD*)	Age *M* (*SD*)	Female (%) (Total)	AMSTAR2 [6]
Tyas et al. [56]	2001	Canada	N-ADRDA	MMSE	>26	CES-D20	≥16	694	3 to 5	65	67	MODERATE
Vilalta-Franch et al. [57]	2013	EU	DSM-IV	CAMCOG	≥79	DSM-IV	-	451	5	76.7 (5.4)	63.7	HIGH
Wilson et al. [58]	2003	USA	N-ADRDA	VARIOUS	-	CES-D10	≥4	142	3.9 (NR)	81.0 (6.6)	52.3	HIGH

Note: Meta-analyses analyzed were: Cherbuin et al. [24], Diniz et al. [22], Gao et al. [23], Kuring et al. [20], Kuring et al. [59], Santabárbara et al. [21]. [1] AD: Alzheimer's disease. DSM-III-R, DSM-IV, DSM-V = Diagnostic and Statistical Manual of Mental Disorders; N-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; N-AIREN = National Institute of Neurological and Communicative Disorders and Stroke–Association Internationale pour la Recherche et l' Enseignement en Neurosciences; ICD-10 = International Classification of Diseases. Total of diagnoses are $k = 30$. [2] Cognitive measures: CERAD/K: Consortium to Establish a Registry for Alzheimer's Disease; MMSE: Mini-Mental State Examination; CRS: Clinical Rating Scale; BIMC: Blessed Information-Memory-Concentration; CASI: Cognitive Abilities Screening Instrument; MSQ: Mental Status Questionnaire; CAMCOG: Cambridge Cognitive Examination. [3] Depression. DSM-III, DSM-III-R, DSM-IV, DSM-V: Diagnostic and Statistical Manual of Mental Disorders; HRSD17: Hamilton M. Rating Scale for DP; GMS-AGECAT: Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy; GDS-15/30: Geriatric Depression Scale; CES/-D10 (10 items)/- D11 (11 items)/-D20 (20 items) = Center for Epidemiologic Studies–DP Scale. [4] Cut-off criteria for categorial depression measures: HRSD-17, Hamilton et al. [60]; Williams et al. [61]; GMS-AGECAT, Copeland et al. [62]; GDS 15/30, Jung et al. [63]; Yesavage et al. [64]; SGDS, Kim et al. [65]; CES-D/D20, Radloff [66]; CES-D10/11, Kohout et al. [67]. [5] Follow-up: Total sample size for controls and healthy indicated; separate sample sizes for those with AD and depression and healthy controls were not reported. Study based on registry data. [6] AMSTAR 2 identifies quality of randomized controlled clinical trials. Rating overall confidence in the results: High = Zero or one non-critical weakness; Moderate = More than one non-critical weakness; Low = One critical flaw with or without non-critical weaknesses; Critically low = More than one critical flaw with or without non-critical weaknesses, Shea et al. [27] (https://amstar.ca/Amstar_Checklist.php accessed on 19 April 2021).

3. Results

The search strategy produced a total of 443 meta-analyses (see Table 1). Initially, 37 meta-analyses were eligible for inclusion. Of these, 31 were excluded: (a) 3 did not report an effect size; (b) 6 did not provide information on the relationship between depression and AD; (c) 8 were duplicates; (d) 9 were systematic reviews about other topics; (e) 4 aimed to study the effect of medication on AD; and (f) 1 included the same primary studies as another. Finally, a total of six meta-analyses were analyzed (k = 28 pooled effect sizes), representing data from n = 28 individual studies (see Figure 1).

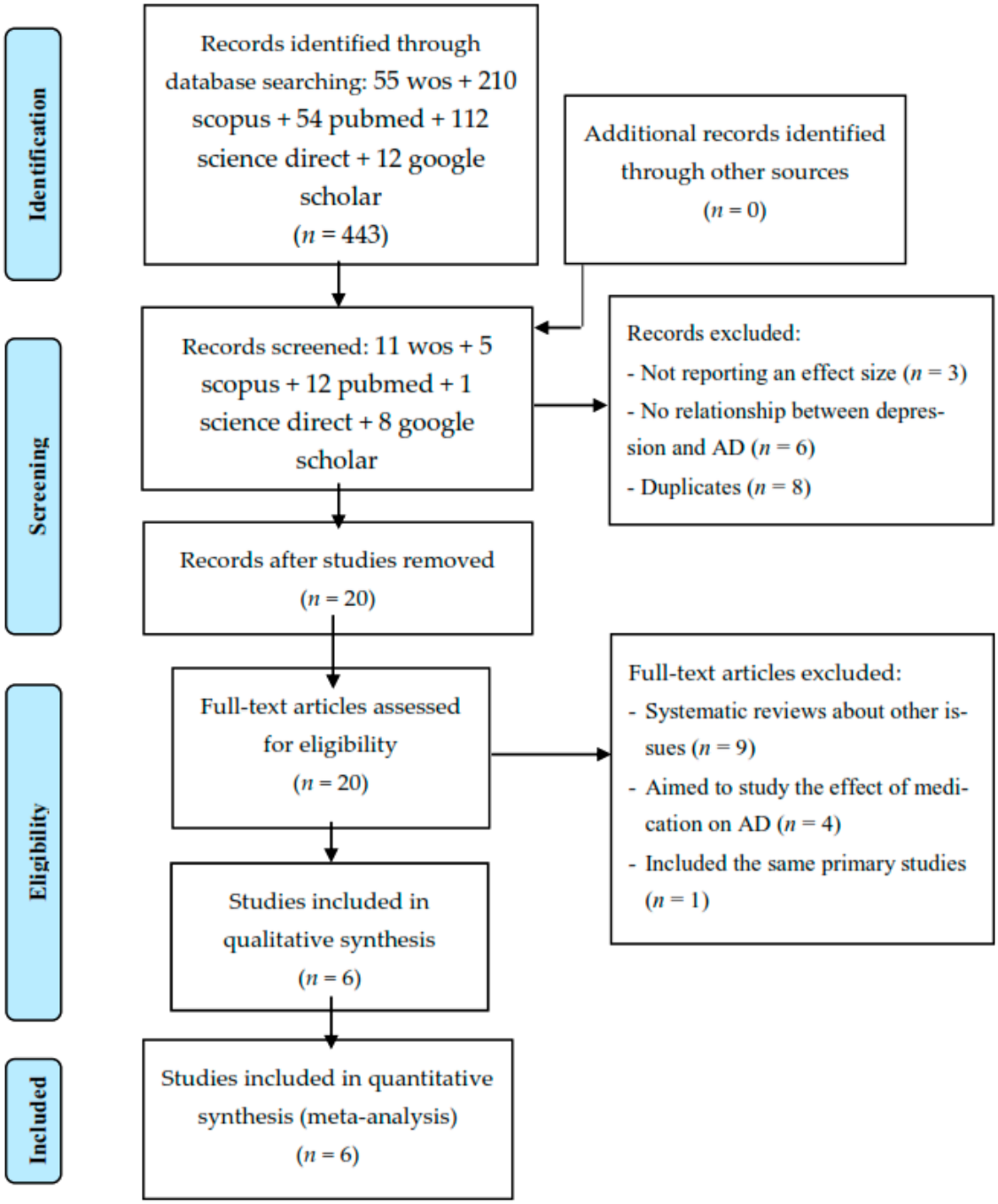

Figure 1. Flow chart depicting the selection of articles for our meta-analysis. Note: AD: alzheimer's disease; n: number of studies.

Since the effect estimated from a biased collection of studies might overestimate the true effect, we assessed the likely extent of this bias and its potential impact on the

conclusions. The result of Egger's test was not significant: The intercept (B0) was 0.53, 95% CI (−1.88 to 2.95), with t = 0.45, df = 26, $p = 0.65$, indicating no publication bias.

3.1. Overall Results from the Meta-Analysis

A total of 28 individual studies reported the association between depression at baseline and AD at follow-up with a total of 101,881 participants (Nbaseline = 51,830; Nfollow-up = 50,051). Individual sample sizes ranged from 60 to 12,083. The majority of subjects was female. The mean age was 71.95, ranging from 52.7 to 81 years. One study did not report gender and age [53]. The mean follow-up length was 4.90 years (range from 1 to 23.6), with one study not reporting the number of years [54]. Characteristics of the 28 individual studies are presented in Table 1.

A total of 17 and 11 studies were based on symptomatic rating scales and clinical criteria to assess depression, respectively: CES-D ($n = 14$) (50%), DSM-III/III-R/IV/V ($n = 8$) (28.6%), GMS-AGECAT ($n = 3$) (10.7%), GDS ($n = 2$) (7.1%), and HAM-D ($n = 1$) (3.6%). AD diagnosis was established based on the N-ADRDA ($n = 17$) (56.7%) or DSMIII-R/IV/V ($n = 10$) (33.3%), ICD10 ($n = 2$) (6.7%), and N-AIREN ($n = 1$) (3.3%) scales.

Risk estimates were pooled across the 28 studies. The random effect of the relationship between depression and AD was significant (OR = 2.46, 95% CI [1.81–3.35], Z = 5.72, $p < 0.001$). Figure 2 shows the forest plot of the effect sizes and their 95% CI. Heterogeneity across studies was substantial (Q-value = 284.53, df = 27, I2 = 90.51, $p < 0.001$), suggesting the presence of potential moderators (Table 2).

Table 2. Summary details for individual studies that examined the risk of dementia (OR) associated with depression.

Study Name	Statistics for Each Study					Exposed (AD)/Total	Exposed (AD)/Total
	Odds Ratio	*Lower Limit*	*Upper Limit*	*Z-Value*	*p-Value*	Cases (Depression)	Controls (No Depression)
Bae et al. [33]	9.84	0.57	170.00	1.57	0.116	9/359	0/181
Bartolini et al. [34]	16.00	3.72	68.76	3.73	<0.001	31/124	2/98
Becker at al. [18]	1.33	0.49	3.65	0.56	0.578	*HR* = 1.33 (0.49–3.65)	
Blasko et al. [35]	1.09	0.77	1.53	0.47	0.637	77/242	122/406
Burke et al. [36]	4.15	3.49	4.94	15.98	<0.001	205/1214	507/10,869
Chen et al. [37]	3.37	1.33	8.54	2.56	0.011	6/52	28/751
Dal Forno et al. [38]	2.63	1.28	5.40	2.63	0.008	*HR* = 2.63 (1.28–5.40)	
Devanand et al. [39]	5.07	3.02	8.52	6.13	<0.001	57/173	25/283
Dotson et al. [40]	1.02	0.77	1.35	0.11	0.911	96/938	125/1239
Fuhrer et al. [41]	1.04	0.69	1.58	0.19	0.849	30/203	196/1373
Gatz et al. [16]	3.49	1.08	11.28	2.09	0.037	*OR* = 3.49 (1.08–11.28)	
Geerlings et al. [42]	2.21	1.09	4.48	2.20	0.028	*OR* = 2.21 (1.09–4.48)	
Geerlings et al. [43]	1.41	0.55	3.58	0.71	0.475	6/35	44/343
Gracia-García et al. [44]	1.81	0.98	3.36	1.89	0.059	13/452	51/3174
Heser et al. [45]	2.70	1.80	4.03	4.84	<0.001	34/306	118/2663
Irie et al. [46]	9.94	3.16	31.22	3.93	<0.001	6/146	6/1397
Kim et al. [47]	1.33	0.62	2.85	0.74	0.463	*HR* = 1.33(0.62–2.85)	
Kim et al. [48]	2.33	0.97	5.56	1.90	0.057	7/45	38/518
Lauriola et al. [49]	130.73	7.90	2162.50	3.40	0.001	57/115	0/66
Lenoir et al. [50]	1.01	0.69	1.49	0.05	0.960	*HR* = 1.0 (0.7–1.6)	
Li et al. [51]	1.43	1.05	1.94	2.28	0.022	*HR* = 1.43 (1,05–1,94)	
Luchsinger et al. [52]	3.40	1.46	7.90	2.85	0.004	*HR* = 3.4 (1.5–8.1)	
Reding et al. [53]	19.00	12.42	29.06	13.59	<0.001	*HR* = 19.00 (12.40–27.90)	
Richard et al. [54]	2.03	1.44	2.86	4.06	<0.001	55/452	109/1708
Saczynski et al. [55]	1.76	1.03	3.01	2.07	0.039	*HR* = 1.76 (1.03–3.01)	
Tyas et al. [56]	2.00	1.01	3.95	2.00	0.046	21/36	271/658
Vilalta-Franch et al. [57]	2.36	1.11	5.03	2.23	0.026	13/116	17/335
Wilson et al. [58]	1.33	1.01	1.76	2.01	0.044	*OR* = 1.33 (1.01–1.76)	
Random effects	2.46	1.81	3.35	5.72	<0.001		

Note: AD: Alzheimer's disease; NO-AD: No Alzheimer's disease. Ns are based on total participant data available for depression or AD (not entire sample). Some data (N at baseline and follow-up) were not available for the depression and control groups, because studies did not provide them. In those cases, we reported the effect given in primary studies.

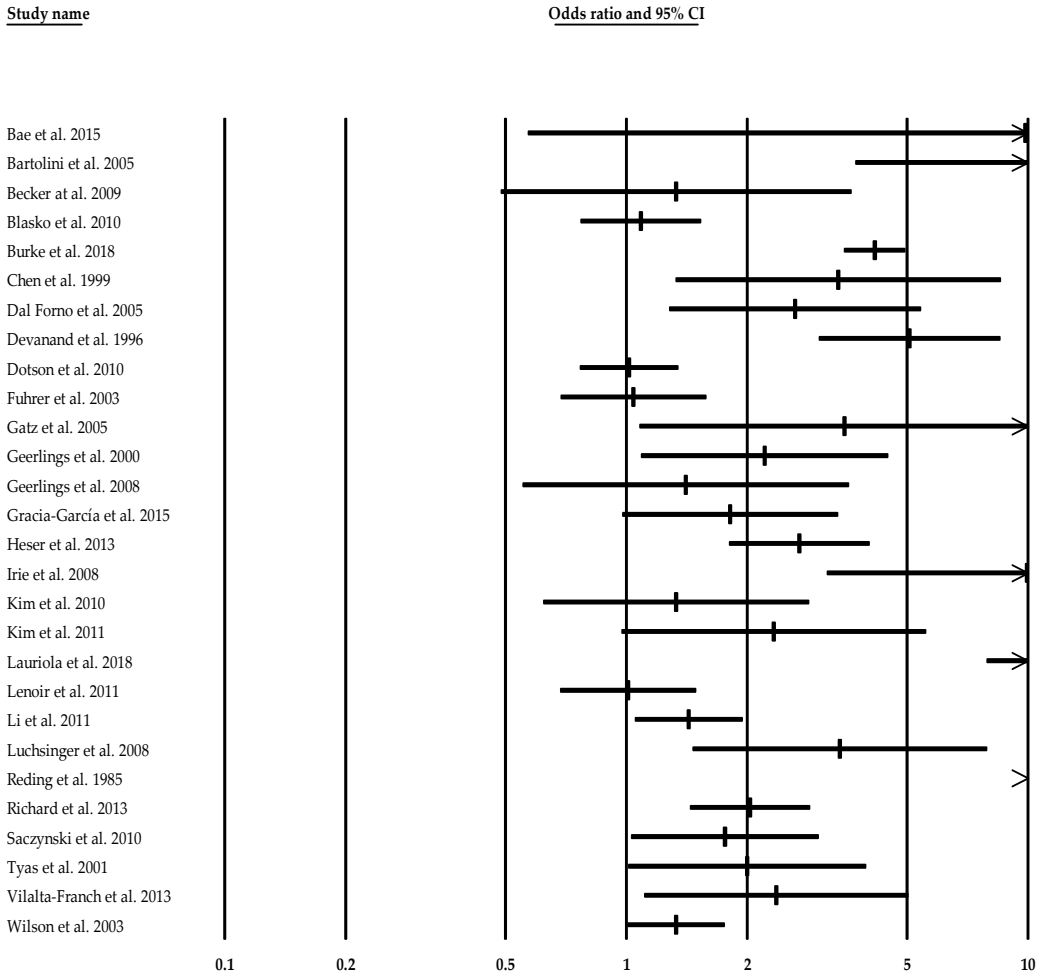

Figure 2. Forest plot of studies investigating the risk of Alzheimer's disease (Time2) associated with depression (including all instruments).

3.2. Clinical Criteria and Symptomatic Rating Scales to Assess Depression

We tested three different models that reflected a combination of methodological moderators (see Table 3). Random effect models revealed a significant positive effect size of the association between depression and risk of AD for clinical (k = 11) and symptomatic (k = 17) measures of depression. Heterogeneity was substantial for the depression criteria (I2 = 90.51), indicating that the OR was greater for clinical than symptomatic measures.

Then, we performed an additional sub-group analysis distinguishing between types of symptomatic rating scale used to assess depression. The total effect (OR) was significant (1.80, 95% CI: 1.16–2.78, Z = 2.62, p = 0.009), and heterogeneity was moderate (I2 = 61.84). Sub-group analysis yielded a significant effect of depression on the development of AD for studies using the CES-D scales and HSRD, although this effect was non-significant when studies used the GDS scale. Only one study included the HSRD scale, and no additional subsample analyses were conducted. However, sufficient data were available for the CES-D (k = 14). We conducted further sub-analyses according to different cut-off points of the CES-D scale to define presence of depression. ORs were pooled across 14 studies (OR = 1.68, IC95% 1.24–2.27, Z = 3.36, p = 0.001). Heterogeneity was moderate across these studies (I2 = 63.95), indicating that the effect of depression on the risk of AD may differ according to the cut-off points used. Estimates were significant for $\geq$10 and $\geq$16 cut-offs, whereas the effect of depression on AD was not significant when studies used a cut-off of $\geq$4 and $\geq$20 (Table 3).

Table 3. Summary effect sizes.

	Model Statistics							
	k	***OR***	***LL***	***UL***	***Z***	***p***	Q_W	Q_B
Depression criteria (model 1)								
Clinic	11	3.68	2.44	5.55	6.20	0.0001	172.78 ***	6.86 **
Symptomatic	17	1.81	1.30	2.53	3.51	0.0001		
Depression scale (model 2)								
GDS	2	1.63	0.64	4.15	1.03	0.303		
CES-D	14	1.60	1.28	2.02	4.07	0.0001	37.83 ***	1.87
HSRD	1	3.40	1.19	9.71	2.29	0.022		
Cut-off (CES-D) (model 3)								
≥4	2	1.63	0.97	2.78	1.80	0.072		
≥10	3	2.02	1.14	3.60	2.39	0.017	28.63 **	1.97
≥16	8	1.44	1.04	2.00	2.19	0.028		
≥20	1	2.63	0.97	7.11	1.91	0.057		

Note: *** $p \leq 0.001$, ** $p \leq 0.01$, k: number of studies; OR: Odds ratio; LL: Lower limit; UL: Upper limit; Q_w: heterogeneity within; Q_b: heterogeneity between.

3.3. Meta Regression Analysis

We conducted a meta-regression analysis to determine whether the criteria used to measure depression might explain differences across studies in reporting effect size and might also cause heterogeneity. A significant negative effect of the use of symptomatic rating scales on the prediction of AD was found (b = −0.71, Se = 0.27, 95% CI: −1.24/−0.17, Z = −2.59, p = 0.009) compared to clinical criteria (k = 28, intercept: b = 1.30, se = 0.21, CI: 0.89/1.72, Z = 6.14, $p \leq 0.001$) (Q = 6.71, df = 1, p = 0.009). Together, these explained 26% of the variance. That is, the use of symptomatic rating scales to assess depression was associated with a decreased likelihood of developing AD in the follow-up compared to the use of clinical criteria.

No significant moderating effects were found in meta-regression analyses conducted for the various symptomatic rating scales of depression (k = 17) (1 = GDS, intercept: b = 0.47, Se = 0.45 (−0.41/1.36), Z = 1.04, p= 0.296; 2. CES-D: b = −0.02, Se = 0.46 (−0.93/0.89), Z = −0.04, p = 0.97; 3. HSRD: b = 0.75, Se = 0.68 (−0.59/2.09), Z = 1.10, p = 0.270) (Q = 2.18, df = 2, p = 0.336). Differences explained the 28% of variation observed in the association between depression and AD.

When analyzing the differential effect of the CES-D cut-offs on the development of AD (k = 14), results showed a greater predictive effect for studies using more restrictive cut-off points (≥20) (intercept: b = 0.97, SE = 0.37, 95% CI: 0.25/1.69, Z = 2.63, p = 0.008) (≥4: b = −0.51, Se = 0.38 (−1.26/0.24), Z = 1.34, p = 0.180; ≥0.10: b = −0.50, SE = 0.39 (−1.27/0.28), Z = −1.26, p = 0.209; ≥0.16: b = −0.77, SE = 0.38 (−1.51/−0.01), Z = −2.04, p = 0.041) (Q = 7.43, df = 3, p = 0.050]. The different cut-off points of the CES-D explained the 53% of variation in the diagnosis of AD (Figure 3).

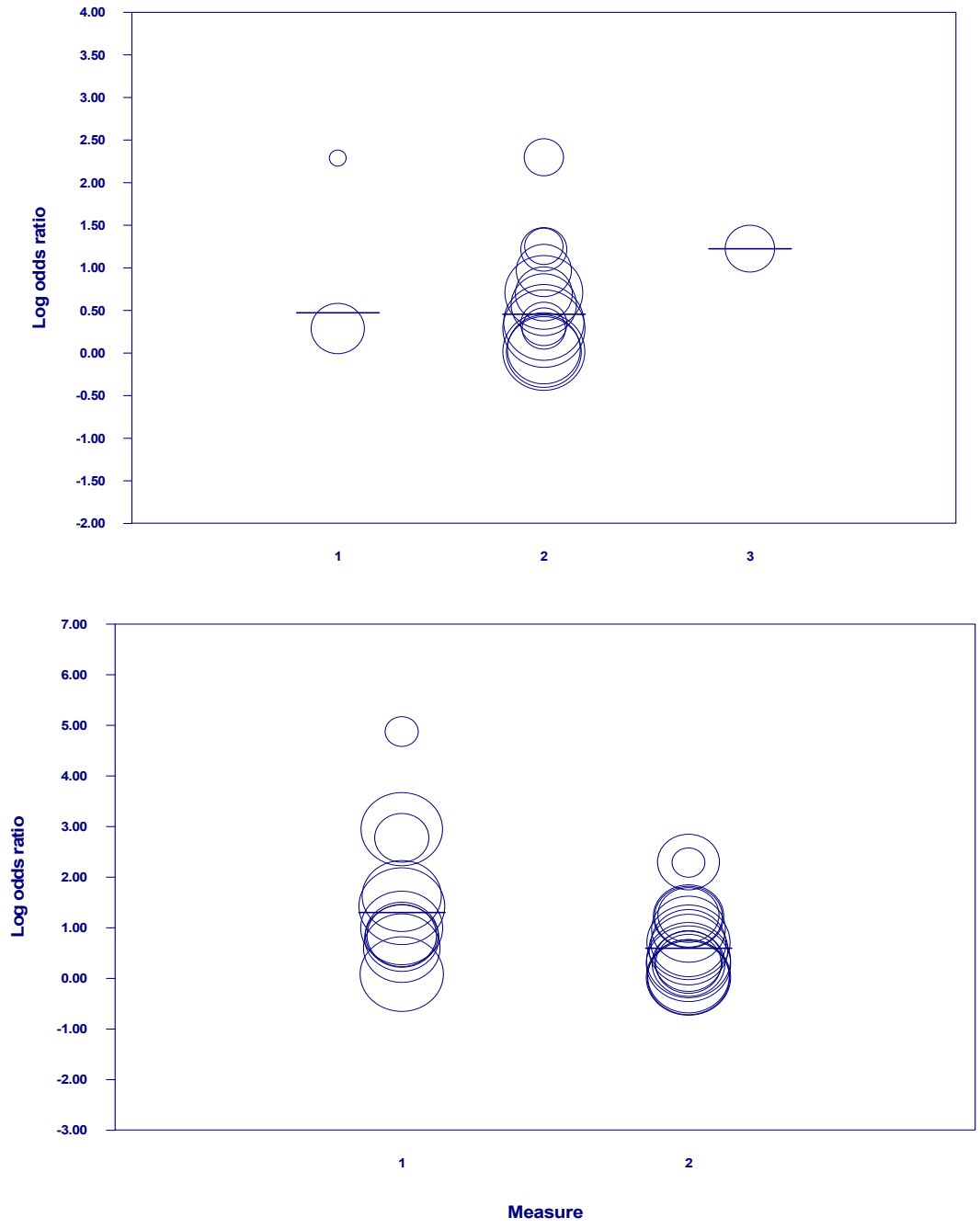

Figure 3. Meta-regression of log odds ratio on type of measure, symptomatic tool, and CES-D cut-offs (95% intervals are simultaneous and based on Z distribution). Scatterplots show the relationship between each covariate and AD.

4. Discussion

The main contribution of this study was to produce precise AD risk estimates associated with different depression criteria, either clinically significant or based on symptomatic scales. Based on the results of 11 cohorts, we found a more than three-fold increased risk of AD for clinically significant depression. Likewise, based on findings of 17 cohort studies, the risk of AD increased almost two-fold in participants diagnosed with symptomatic measures of depression. We found that studies that used clinically significant criteria for diagnosis of depression had more consistent and significant results than those that used symptomatic scales.

However, most included studies used self-reported symptomatic scales for diagnosis of depression, specifically the CES-D. We further analyzed the differential effect of CES-D

cut-off points on AD risk and found that they explained 53% of the variability of results. We found a slightly significant predictive effect in meta-analyzed data of studies using the cut-off CES-D point ≥10 and ≥16, but predictive risk of AD was greater for one study using a more restrictive cut-off point (≥20). Our results are consistent with those of Cherbuin et al. [24] who found that the meta-analysis of studies using a cut-off previously validated against clinical criteria (≥20) demonstrated higher risk estimates than those using a more lenient cut-off (≥16).

We found a greater effect of clinically significant depression on AD risk than the MA of Santabárbara et al. [21], probably because that meta-study included only three studies with homogeneous criteria for the diagnosis of depression (GMS-AGECAT). We also included eight studies using DSM criteria for depression; all of them but one, Blasko et al. [35], found consistently higher risk of AD compared to any other criteria. However, some of them found relatively large [34,53] or even extreme values of OR [49].

Furthermore, our study includes recent references [20], and it did not analyze data from studies of patient groups with mixed psychiatric histories or all types of dementia. Even though the meta-analysis of Kuring et al. [20] analyzed 36 independent studies for all types of dementia, they only pooled k = 8 studies for AD (OR = 2.23). This inclusion criterion may explain why our results show a greater OR risk from depression to AD than previous meta-analyses [20–24]. Furthermore, they did not analyze variability arising from the type of measure (clinical or symptomatic criteria) and from cut-off points used to assess depression across studies. Another strength of our study is that it includes a selection of prospective cohort studies to provide more evidence in establishing the cause and effect, and the relationship between depression and AD [21]. We analyzed a long follow-up period (4.9 years, range 1–23.6 years) to observe the potential association between depression (as an antecedent) and risk of AD, avoiding cross-sectional studies [20,24]. This analysis covers a gap in the previous literature, adding new information about the association between depression and AD. Finally, previous meta-analyses limited the literature search to biomedical databases. In our study, we included five databases in order to provide coverage of publications from different countries, reducing the likelihood of publication bias [22,23].

Overall, our study is the first to review all previously available meta-analyses of depression as a risk factor of incident AD systematically. Moreover, we included individual studies when they assessed clinically significant depression or a validated cut-off score in a symptomatic depression scale, and we conducted differential meta-analysis of specific AD risk estimates according to depression criteria. Our study demonstrates how depression criteria can explain variability between studies in the association between depression and incident AD. We agree with Cherbuin et al. [24] about the importance of using objective and specific measures of risk in evidence-based clinical practice.

A number of different hypotheses on the association between depression and dementia were suggested, yet the ways in which depression influences AD are as yet unclear. For instance, antidepressant use (i.e., anticholinergic drugs) was shown to be associated with an increased risk of dementia [68–71]. Furthermore, the ε4 allele of apolipoprotein E (APOE) was associated with the development of AD [46,47]. However, the idea that ε4 and dementia may be linked has little support [72–75]. In this vein, some risk factors, such as brain-vascular [76], cortisol, hippocampal atrophy [77], and neuroinflammation, could involve a possible common pathway to explain the association between depression and AD [78].

We should also recognize some limitations of our study. Firstly, as the studies included in the meta-analyses reported either the odds ratio or the hazard ratio for the association between late-life depression and dementia, we calculated the pooled OR for the association between depression and AD separately. Odds ratio is a measure of association between two conditions (such as in logistic regression models), whereas the hazard ratio is a measure of the strength of the association between two conditions in time-to-event statistical analysis. Given this, we should interpret the results from the pooled risk analysis with caution, as

we included studies that reported hazard ratios and odds ratios together. Nonetheless, the results are very consistent across all analyses for AD. Secondly, individual studies assessing depressive symptoms by self-rating scales used pre-established cut-off scores, and no structured interviews were conducted for the diagnosis of depressive disorders, which may have introduced significant heterogeneity into the classification of cases and non-cases, in particular in individuals with mild depression; according our results, this may explain a good deal of the variability in results between studies. In addition, some of the studies included in this meta-analysis were not representative of the entire population (such as studies including only men) [46]. Although we did not find a moderator effect of observation time (results not shown), and the results support the hypothesis that clinical depression is a risk factor for later development of Alzheimer's disease, the influence of prodromal symptoms should not be discounted, and it remains to be determined. Furthermore, we did not examine the influence of any single study on the overall risk estimates with sensitive analysis that omitted them one by one. Moreover, by choosing to include studies that allowed us to calculate crude ORs, we implicitly included studies that provided estimates of the relation between depression and AD risk in the form of unadjusted ORs, so other study-related factors may have affected the outcomes of these studies (age or sex). Inclusion of these studies may have biased our results. Another possible limitation of this meta-analysis is that our search was limited to certain databases. We did a careful review of all references in potentially relevant publications, previous meta-analyses, and systematic reviews published on depression and AD. Nevertheless, a search of other international databases (such as EMBASE and PsycINFO) might have led to the identification of additional studies that could have been included in this meta-analysis.

5. Conclusions

Although we cannot yet assert an etiological basis of the association, our study provides consistent data pointing to an increased risk of AD for clinically significant depression. Our findings highlight the importance of using more stringent and objective measures of depression in future studies. Depression should be assessed by clinicians with standardized, validated measures, and preventive strategies targeting at-risk individuals should be designed. Further studies need to assess the potential for treatment of clinically significant depression to decrease the risk of AD.

Author Contributions: All authors take full responsibility for the data, analysis, and interpretation, and the conducting of the research, and had full access to all of the data and the right to publish any and all data. The contributions of each author are as follows: O.S.-V. conceived and designed the analysis, collected the data, contributed data or analysis tools, performed analysis, and wrote the paper; P.G.-G. helped write the paper; S.U.-L. contributed data and analysis tools, performed analysis, and helped write the paper; A.P.-M. conceived and designed the analysis, collected the data, contributed data and analysis tools, performed analysis, and helped write the paper; S.C.-Y., B.O., and J.S. helped write the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by Grants from the Fondo de Investigación Sanitaria, Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness, Madrid, Spain (grants 94/1562, 97/1321E, 98/0103, 01/0255, 03/0815, 06/0617, 12/02254, 16/00896, PI/19/01874, G03/128) and from the Fondo Europeo de Desarrollo Regional (FEDER) of the European Union "Una manera de hacer Europa" (Project number PI16/00896) and Gobierno de Aragón (grant B15_17R). BO's work is supported by the Miguel Servet program (CP20/00040), funded by the Instituto de Salud Carlos III and co-funded by the European Union (ERDF/ESF, "Investing in your future"). This study was partially supported by FEDER funds and the Spanish Ministry of Economy and Competitiveness (Projects ECO2016-76567-C4-2-R and PID2019-104263RB-C44), the Regional Government of "Castilla y León", Spain (Project BU329U14 and BU071G19), the Regional Government of "Castilla y León", and FEDER funds (Project BU062U16).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: We declare that P.G.-G. has received financial support to attend scientific meetings from Servier, Pfizer, Lundbeck, Nutrición Médica, and Esteve. None of these activities is related to the current project. For the remaining authors, no conflicts of interest are declared.

References

1. Villain, N.; Dubois, B. Alzheimer's Disease Including Focal Presentations. *Semin. Neurol.* **2019**, *39*, 213–226. [CrossRef]
2. Huang, L.-K.; Chao, S.-P.; Hu, C.-J. Clinical trials of new drugs for Alzheimer disease. *J. Biomed. Sci.* **2020**, *27*, 1–13. [CrossRef] [PubMed]
3. De la Salud, A.M. *Proyecto de Plan de Acción Mundial Sobre La Respuesta de Salud Pública a La Demencia: Informe de La Directora General*; WHO: Geneva, Switzerland, 2017.
4. Niu, H.; Álvarez-Álvarez, I.; Guillén-Grima, F.; Aguinaga-Ontoso, I. Prevalencia e incidencia de la enfermedad de Alzheimer en Europa: Metaanálisis. *Neurología* **2017**, *32*, 523–532. [CrossRef]
5. Selkoe, D.J. Alzheimer disease and aducanumab: Adjusting our approach. *Nat. Rev. Neurol.* **2019**, *15*, 365–366. [CrossRef] [PubMed]
6. Harris, J.R. *Protein Aggregation and Fibrillogenesis in Cerebral and Systemic Amyloid Disease*; Springer Science and Business Media: Berlin/Heidelberg, Germany, 2012; Volume 65, ISBN 94-007-5416-7.
7. Migliaccio, R.; Agosta, F.; Rascovsky, K.; Karydas, A.; Bonasera, S.; Rabinovici, G.D.; Miller, B.L.; Gorno-Tempini, M.L. Clinical syndromes associated with posterior atrophy: Early age at onset AD spectrum. *Neurology* **2009**, *73*, 1571–1578. [CrossRef]
8. Surguchov, A. Caveolin: A New Link Between Diabetes and AD. *Cell. Mol. Neurobiol.* **2020**, *40*, 1059–1066. [CrossRef] [PubMed]
9. Tsuno, N.; Homma, A. What is the association between depression and Alzheimer's disease? *Expert Rev. Neurother.* **2009**, *9*, 1667–1676. [CrossRef] [PubMed]
10. WHO. *Depression and Other Common Mental Disorders: Global Health Estimates*; World Health Organization: Geneva, Switzerland, 2017; pp. 1–24.
11. Drevets, W.C.; Rubin, E.H. Psychotic symptoms and the longitudinal course of senile dementia of the Alzheimer type. *Biol. Psychiatry* **1989**, *25*, 39–48. [CrossRef]
12. Lyketsos, C.G.; Tune, L.E.; Pearlson, G.; Steele, C. Major Depression in Alzheimer's Disease. *Psychosomatics* **1996**, *37*, 380–384. [CrossRef]
13. De Oliveira, F.; Bertolucci, P.F.; Chen, E.; Smith, M. Assessment of risk factors for earlier onset of sporadic Alzheimer's disease dementia. *Neurol. India* **2014**, *62*, 625. [CrossRef]
14. Cantón-Habas, V.; Rich-Ruiz, M.; Romero-Saldaña, M.; Carrera-González, M.D.P. Depression as a Risk Factor for Dementia and Alzheimer's Disease. *Biomedicines* **2020**, *8*, 457. [CrossRef]
15. Kuo, C.-Y.; Stachiv, I.; Nikolai, T. Association of Late Life Depression, (Non-) Modifiable Risk and Protective Factors with Dementia and Alzheimer's Disease: Literature Review on Current Evidences, Preventive Interventions and Possible Future Trends in Prevention and Treatment of Dementia. *Int. J. Environ. Res. Public Health* **2020**, *17*, 7475. [CrossRef]
16. Gatz, J.L.; Tyas, S.L.; John, P.S.; Montgomery, P. Do Depressive Symptoms Predict Alzheimer's Disease and Dementia? *J. Gerontol. Ser. A Boil. Sci. Med. Sci.* **2005**, *60*, 744–747. [CrossRef]
17. Tapiainen, V.; Hartikainen, S.; Taipale, H.; Tiihonen, J.; Tolppanen, A.-M. Hospital-treated mental and behavioral disorders and risk of Alzheimer's disease: A nationwide nested case-control study. *Eur. Psychiatry* **2017**, *43*, 92–98. [CrossRef]
18. Becker, J.T.; Chang, Y.-F.; Lopez, O.L.; Dew, M.A.; Sweet, R.A.; Barnes, D.; Yaffe, K.; Young, J.; Kuller, L.; Reynolds, C.F. Depressed Mood is Not a Risk Factor for Incident Dementia in a Community-Based Cohort. *Am. J. Geriatr. Psychiatry* **2009**, *17*, 653–663. [CrossRef]
19. Hudon, C.; Escudier, F.; De Roy, J.; Croteau, J.; Cross, N.; Dang-Vu, T.T.; Zomahoun, H.T.V.; Grenier, S.; Gagnon, J.-F.; Parent, A.; et al. Behavioral and Psychological Symptoms that Predict Cognitive Decline or Impairment in Cognitively Normal Middle-Aged or Older Adults: A Meta-Analysis. *Neuropsychol. Rev.* **2020**, *30*, 558–579. [CrossRef]
20. Kuring, J.; Mathias, J.; Ward, L. Risk of Dementia in persons who have previously experienced clinically-significant Depression, Anxiety, or PTSD: A Systematic Review and Meta-Analysis. *J. Affect. Disord.* **2020**, *274*, 247–261. [CrossRef]
21. Serrano, J.S.; Pérez, A.S.; Olaya, B.; García, P.G.; Antón, R.L. Depresión tardía clínicamente relevante y riesgo de demencia: Revisión sistemática y metaanálisis de estudios prospectivos de cohortes. *Revista de Neurología* **2019**, *68*, 493–502. [CrossRef] [PubMed]
22. Diniz, B.S.; Butters, M.A.; Albert, S.M.; Dew, M.A.; Reynolds, C.F. Late-life depression and risk of vascular dementia and Alzheimer's disease: Systematic review and meta-analysis of community-based cohort studies. *Br. J. Psychiatry* **2013**, *202*, 329–335. [CrossRef] [PubMed]
23. Gao, Y.; Huang, C.; Zhao, K.; Ma, L.; Qiu, X.; Zhang, L.; Xiu, Y.; Chen, L.; Lu, W.; Huang, C.; et al. Retracted: Depression as a risk factor for dementia and mild cognitive impairment: A meta-analysis of longitudinal studies. *Int. J. Geriatr. Psychiatry* **2012**, *28*, 441–449. [CrossRef] [PubMed]
24. Cherbuin, N.; Kim, S.; Anstey, K.J. Dementia risk estimates associated with measures of depression: A systematic review and meta-analysis. *BMJ Open* **2015**, *5*, e008853. [CrossRef] [PubMed]
25. PRISMA Declaration: A Proposal to Improve the Publication of Systematic Reviews and Meta-Analyses. Available online: https://europepmc.org/article/med/20206945 (accessed on 16 February 2020).

26. Shea, B.J.; Grimshaw, J.M.; Wells, A.G.; Boers, M.; Andersson, N.; Hamel, C.; Porter, A.C.; Tugwell, P.; Moher, D.; Bouter, L.M. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. *BMC Med. Res. Methodol.* **2007**, *7*, 10. [CrossRef]
27. Shea, B.J.; Hamel, C.; Wells, G.A.; Bouter, L.M.; Kristjansson, E.; Grimshaw, J.; Henry, D.A.; Boers, M. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J. Clin. Epidemiol.* **2009**, *62*, 1013–1020. [CrossRef] [PubMed]
28. Lipsey, M.W.; Wilson, D.B. *Practical Meta-Analysis*; SAGE Publications, Inc.: Thousand Oaks, CA, USA, 2001; ISBN 0-7619-2167-2.
29. Shrier, I.; Steele, R. Understanding the Relationship Between Risks and Odds Ratios. *Clin. J. Sport Med.* **2006**, *16*, 107–110. [CrossRef] [PubMed]
30. Borenstein, M.; Hedges, L.; Higgins, J.P.T.; Rothstein, H. *Comprehensive Meta-Analysis*; Version 3; Biostat: Englewood, NJ, USA, 2013.
31. Borenstein, M.; Hedges, L.V.; Higgins, J.P.T.; Rothstein, H.R. *Introduction to Meta-Analysis*; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2009; p. 452.
32. Reis, H.T.; Judd, C.M. *Handbook of Research Methods in Social and Personality Psychology*; Cambridge University Press: Cambridge, UK, 2000.
33. Bin Bae, J.; Kim, Y.J.; Ghang, J.H.; Kim, T.H.; Park, J.H.; Lee, S.B.; Lee, J.J.; Jeong, H.G.; Kim, J.L.; Jhoo, J.H.; et al. Incidence of and Risk Factors for Alzheimer's Disease and Mild Cognitive Impairment in Korean Elderly. *Dement. Geriatr. Cogn. Disord.* **2015**, *39*, 105–115. [CrossRef]
34. Bartolini, M.; Coccia, M.; Luzzi, S.; Provinciali, L.; Ceravolo, M.G. Motivational Symptoms of Depression Mask Preclinical Alzheimer's Disease in Elderly Subjects. *Dement. Geriatr. Cogn. Disord.* **2004**, *19*, 31–36. [CrossRef]
35. Blasko, I.; Kemmler, G.; Jungwirth, S.; Wichart, I.; Krampla, W.; Weissgram, S.; Jellinger, K.; Tragl, K.H.; Fischer, P. Plasma Amyloid Beta-42 Independently Predicts Both Late-Onset Depression and Alzheimer Disease. *Am. J. Geriatr. Psychiatry* **2010**, *18*, 973–982. [CrossRef]
36. Burke, S.L.; Cadet, T.; Alcide, A.; O'Driscoll, J.; Maramaldi, P. Psychosocial risk factors and Alzheimer's disease: The associative effect of depression, sleep disturbance, and anxiety. *Aging Ment. Health* **2018**, *22*, 1577–1584. [CrossRef]
37. Chen, P.; Ganguli, M.; Mulsant, B.H.; DeKosky, S.T. The Temporal Relationship Between Depressive Symptoms and Dementia. *Arch. Gen. Psychiatry* **1999**, *56*, 261–266. [CrossRef]
38. Forno, G.D.; Palermo, M.T.; Donohue, J.E.; Karagiozis, H.; Zonderman, A.B.; Kawas, C.H. Depressive symptoms, sex, and risk for Alzheimer's disease. *Ann. Neurol.* **2005**, *57*, 381–387. [CrossRef]
39. Devanand, D.P.; Sano, M.; Tang, M.-X.; Taylor, S.; Gurland, B.J.; Wilder, D.; Stern, Y.; Mayeux, R. Depressed Mood and the Incidence of Alzheimer's Disease in the Elderly Living in the Community. *Arch. Gen. Psychiatry* **1996**, *53*, 175–182. [CrossRef]
40. Dotson, V.M.; Beydoun, M.A.; Zonderman, A.B. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology* **2010**, *75*, 27–34. [CrossRef]
41. Fuhrer, R.; Dufouil, C.; Dartigues, J.F.; For the PAQUID Study. Exploring Sex Differences in the Relationship Between Depressive Symptoms and Dementia Incidence: Prospective Results From the PAQUID Study. *J. Am. Geriatr. Soc.* **2003**, *51*, 1055–1063. [CrossRef] [PubMed]
42. Geerlings, M.I.; Bouter, L.M.; Schoevers, R.; Beekman, A.T.F.; Jonker, C.; Deeg, D.J.H.; Van Tilburg, W.; Adèr, H.J.; Schmand, B. Depression and risk of cognitive decline and Alzheimer's disease. *Br. J. Psychiatry* **2000**, *176*, 568–575. [CrossRef]
43. Geerlings, M.I.; Heijer, T.D.; Koudstaal, P.J.; Hofman, A.; Breteler, M. History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. *Neurology* **2008**, *70*, 1258–1264. [CrossRef]
44. Gracia-García, P.; De-La-Cámara, C.; Santabárbara, J.; Lopez-Anton, R.; Quintanilla, M.A.; Ventura, T.; Marcos, G.; Campayo, A.; Saz, P.; Lyketsos, C.; et al. Depression and Incident Alzheimer Disease: The Impact of Disease Severity. *Am. J. Geriatr. Psychiatry* **2015**, *23*, 119–129. [CrossRef]
45. Heser, K.; Tebarth, F.; Wiese, B.; Eisele, M.; Bickel, H.; Kohler, M.; Mosch, E.; Weyerer, S.; Werle, J.; König, H.-H.; et al. Age of major depression onset, depressive symptoms, and risk for subsequent dementia: Results of the German Study on Ageing, Cognition, and Dementia in Primary Care Patients (AgeCoDe). *Psychol. Med.* **2012**, *43*, 1597–1610. [CrossRef]
46. Irie, F.; Masaki, K.H.; Petrovitch, H.; Abbott, R.D.; Ross, G.W.; Taaffe, D.R.; Launer, L.J.; White, L.R. Apolipoprotein E ε4 Allele Genotype and the Effect of Depressive Symptoms on the Risk of Dementia in Men. *Arch. Gen. Psychiatry* **2008**, *65*, 906–912. [CrossRef]
47. Kim, J.-M.; Kim, S.-Y.; Bae, K.-Y.; Kim, S.-W.; Shin, I.-S.; Yang, S.-J.; Song, Y.-H.; Yoon, J.-S. Apolipoprotein E4 Genotype and Depressive Symptoms as Risk Factors for Dementia in an Older Korean Population. *Psychiatry Investig.* **2010**, *7*, 135–140. [CrossRef]
48. Kim, J.-M.; Stewart, R.; Kim, S.-Y.; Kim, S.-W.; Bae, K.-Y.; Yang, S.-J.; Shin, I.-S.; Yoon, J.-S. Synergistic associations of depression and apolipoprotein E genotype with incidence of dementia. *Int. J. Geriatr. Psychiatry* **2010**, *26*, 893–898. [CrossRef]
49. Lauriola, M.; Mangiacotti, A.; D'Onofrio, G.; Cascavilla, L.; Paris, F.; Ciccone, F.; Greco, M.; Paroni, G.; Seripa, D.; Greco, A. Late-Life Depression versus Amnestic Mild Cognitive Impairment: Alzheimer's Disease Incidence in 4 Years of Follow-Up. *Dement. Geriatr. Cogn. Disord.* **2018**, *46*, 140–153. [CrossRef]
50. Lenoir, H.; Dufouil, C.; Auriacombe, S.; Lacombe, J.-M.; Dartigues, J.-F.; Ritchie, K.; Tzourio, C. Depression History, Depressive Symptoms, and Incident Dementia: The 3C Study. *J. Alzheimer's Dis.* **2011**, *26*, 27–38. [CrossRef]

51. Li, G. Temporal Relationship Between Depression and Dementia. *Arch. Gen. Psychiatry* **2011**, *68*, 970–977. [CrossRef] [PubMed]
52. Luchsinger, J.A.; Reitz, C.; Honig, L.S.; Tang, M.-X.; Shea, S.; Mayeux, R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology* **2005**, *65*, 545–551. [CrossRef]
53. Reding, M.; Haycox, J.; Blass, J. Depression in Patients Referred to a Dementia Clinic. *Arch. Neurol.* **1985**, *42*, 894–896. [CrossRef]
54. Richard, E.; Reitz, C.; Honig, L.H.; Schupf, N.; Tang, M.X.; Manly, J.J.; Mayeux, R.; Devanand, D.; Luchsinger, J.A. Late-Life Depression, Mild Cognitive Impairment, and Dementia. *JAMA Neurol.* **2013**, *70*, 380–382. [CrossRef]
55. Saczynski, J.S.; Beiser, A.; Seshadri, S.; Auerbach, S.; Wolf, P.A.; Au, R. Depressive symptoms and risk of dementia: The Framingham Heart Study. *Neurology* **2010**, *75*, 35–41. [CrossRef]
56. Tyas, S.L.; Manfreda, J.; A Strain, L.; Montgomery, P.R. Risk factors for Alzheimer's disease: A population-based, longitudinal study in Manitoba, Canada. *Int. J. Epidemiol.* **2001**, *30*, 590–597. [CrossRef]
57. Vilalta-Franch, J.; López-Pousa, S.; Llinàs-Reglà, J.; Calvó-Perxas, L.; Merino-Aguado, J.; Garre-Olmo, J. Depression subtypes and 5-year risk of dementia and Alzheimer disease in patients aged 70 years. *Int. J. Geriatr. Psychiatry* **2012**, *28*, 341–350. [CrossRef]
58. Wilson, R.; Schneider, J.; Bienias, J.; Arnold, S.; Evans, D.; Bennett, D. Depressive symptoms, clinical AD, and cortical plaques and tangles in older persons. *Neurology* **2003**, *61*, 1102–1107. [CrossRef]
59. Kuring, J.K.; Mathias, J.L.; Ward, L. Prevalence of Depression, Anxiety and PTSD in People with Dementia: A Systematic Review and Meta-Analysis. *Neuropsychol. Rev.* **2018**, *28*, 393–416. [CrossRef]
60. Hamilton, M. Development of a Rating Scale for Primary Depressive Illness. *Br. J. Soc. Clin. Psychol.* **1967**, *6*, 278–296. [CrossRef]
61. Williams, J.B.W. A Structured Interview Guide for the Hamilton Depression Rating Scale. *Arch. Gen. Psychiatry* **1988**, *45*, 742–747. [CrossRef]
62. Copeland, J.R.M.; Dewey, M.E.; Griffiths-Jones, H.M. A computerized psychiatric diagnostic system and case nomenclature for elderly subjects: GMS and AGECAT. *Psychol. Med.* **1986**, *16*, 89–99. [CrossRef] [PubMed]
63. Jung, I.K.; Kwak, D.I.; Joe, S.H.; Lee, H.S. A Study of Standardization of Korean Form of Geriatric Depression Scale (KGDS). *J. Korean Geriatr. Psychiatry* **1997**, *1*, 61–72.
64. Yesavage, J.A.; Brink, T.; Rose, T.L.; Lum, O.; Huang, V.; Adey, M.; Leirer, V.O. Development and validation of a geriatric depression screening scale: A preliminary report. *J. Psychiatr. Res.* **1982**, *17*, 37–49. [CrossRef]
65. Kim, J.Y.; Park, J.H.; Lee, J.J.; Huh, Y.; Lee, S.B.; Han, S.K.; Choi, S.W.; Lee, N.Y.; Kim, K.W.; Woo, J.I. Standardization of the Korean Version of the Geriatric Depression Scale: Reliability, Validity, and Factor Structure. *Psychiatry Investig.* **2008**, *5*, 232–238. [CrossRef]
66. Radloff, L.S. The CES-D Scale. *Appl. Psychol. Meas.* **1977**, *1*, 385–401. [CrossRef]
67. Kohout, F.J.; Berkman, L.F.; Evans, D.A.; Cornoni-Huntley, J. Two Shorter Forms of the CES-D Depression Symptoms Index. *J. Aging Health* **1993**, *5*, 179–193. [CrossRef] [PubMed]
68. Green, R.C.; Cupples, L.A.; Kurz, A.; Auerbach, S.; Go, R.; Sadovnick, D.; Duara, R.; Kukull, W.A.; Chui, H.; Edeki, T.; et al. Depression as a Risk Factor for Alzheimer Disease. *Arch. Neurol.* **2003**, *60*, 753–759. [CrossRef] [PubMed]
69. Kessing, L.V.; Søndergård, L.; Forman, J.L.; Andersen, P.K. Antidepressants and dementia. *J. Affect. Disord.* **2009**, *117*, 24–29. [CrossRef]
70. Richardson, K.; Fox, C.; Maidment, I.; Steel, N.; Loke, Y.K.; Arthur, A.; Myint, P.K.; Grossi, C.M.; Mattishent, K.; Bennett, K.; et al. Anticholinergic drugs and risk of dementia: Case-control study. *BMJ* **2018**, *361*, k1315. [CrossRef]
71. Wang, C.; Gao, S.; Hendrie, H.C.; Kesterson, J.; Campbell, N.L.; Shekhar, A.; Callahan, C.M. Antidepressant Use in the Elderly Is Associated with an Increased Risk of Dementia. *Alzheimer's Dis. Assoc. Disord.* **2016**, *30*, 99–104. [CrossRef] [PubMed]
72. Henderson, A.S.; Korten, A.E.; Jacomb, P.A.; MacKinnon, A.J.; Jorm, A.F.; Christensen, H.; Rodgers, B. The course of depression in the elderly: A longitudinal community-based study in Australia. *Psychol. Med.* **1997**, *27*, 119–129. [CrossRef]
73. Class, C.A.; Unverzagt, F.W.; Gao, S.; Sahota, A.; Hall, K.S.; Hendrie, H.C. The association between Apo E genotype and depressive symptoms in elderly African-American subjects. *Am. J. Geriatr. Psychiatry* **1997**, *5*, 339–343. [CrossRef] [PubMed]
74. Forsell, Y.; Corder, E.H.; Basun, H.; Lannfelt, L.; Viitanen, M.; Winblad, B. Depression and dementia in relation to apolipoprotein E polymorphism in a population sample age 75+. *Biol. Psychiatry* **1997**, *42*, 898–903. [CrossRef]
75. Zubenko, G.S.; Henderson, R.; Stiffler, J.S.; Stabler, S.; Rosen, J.; Kaplan, B.B. Association of the APOE ε4 allele with clinical subtypes of late life depression. *Biol. Psychiatry* **1996**, *40*, 1008–1016. [CrossRef]
76. Puy, L.; Jouvent, E. Accidente cerebrovascular en el paciente anciano. *EMC Tratado de Medicina* **2020**, *24*, 1–6. [CrossRef]
77. Ouanes, S.; Popp, J. High Cortisol and the Risk of Dementia and Alzheimer's Disease: A Review of the Literature. *Front. Aging Neurosci.* **2019**, *11*, 43. [CrossRef]
78. Hong, H.; Kim, B.S.; Im, H.-I. Pathophysiological Role of Neuroinflammation in Neurodegenerative Diseases and Psychiatric Disorders. *Int. Neurourol. J.* **2016**, *20*, 52–57. [CrossRef] [PubMed]

frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 11 January 2023
DOI 10.3389/fneur.2022.1065335

OPEN ACCESS

EDITED BY
Anna Maria Lavezzi,
University of Milan, Italy

REVIEWED BY
Alan Lerner,
University Hospitals Cleveland Medical Center, United States
Pan Li,
Tianjin Huanhu Hospital, China

*CORRESPONDENCE
Silvia Ubillos-Landa
✉ subillos@ubu.es

SPECIALTY SECTION
This article was submitted to Dementia and Neurodegenerative Diseases, a section of the journal Frontiers in Neurology

RECEIVED 09 October 2022
ACCEPTED 21 December 2022
PUBLISHED 11 January 2023

CITATION
Sáiz-Vazquez O, Puente-Martínez A, Pacheco-Bonrostro J and Ubillos-Landa S (2023) Blood pressure and Alzheimer's disease: A review of meta-analysis.
Front. Neurol. 13:1065335.
doi: 10.3389/fneur.2022.1065335

Blood pressure and Alzheimer's disease: A review of meta-analysis

Olalla Sáiz-Vazquez[1], Alicia Puente-Martínez[2], Joaquín Pacheco-Bonrostro[3] and Silvia Ubillos-Landa[4]*

[1]Department of Occupational Therapy, Faculty of Health Science, University of Burgos, Burgos, Spain, [2]Department of Social Psychology and Anthropology, Faculty of Social Sciences, University of Salamanca (USAL), Salamanca, Spain, [3]Department of Applied Economy, Faculty of Economics and Business Sciences, University of Burgos, Burgos, Spain, [4]Department of Social Psychology, Faculty of Health Science, University of Burgos, Burgos, Spain

Background: Alzheimer's disease (AD) is a neurological disorder of unknown cause, resulting in the death of brain cells. Identifying some of the modifiable risk factors for AD could be crucial for primary prevention and could lead to a reduction in the incidence of AD.

Objective: This study aimed to perform a meta-meta-analysis of studies in order to assess the effect of blood pressure (BP) on the diagnosis of AD.

Method: The search was restricted to meta-analyses assessing high systolic BP (SBP) and diastolic BP (DBP) and AD. We applied the PRISMA guidelines.

Results: A total of 214 studies were identified from major databases. Finally, five meta-analyses (52 studies) were analyzed in this review. Results confirm that high SBP is associated with AD. The exploration of parameters (sex, age, study design, region, and BP measurements) shows that only region significantly moderates the relationship between BP and AD. Asian people are those whose SBP levels >140 mmHg are associated with AD. BP is associated with AD in both people aged ≤65 years and those aged ≥65 years and in cross-sectional and longitudinal studies. In the case of DBP, only women are at a higher risk of AD, particularly when its levels are >90.

Conclusion: SBP is associated with both cerebrovascular disease and AD. Therefore, future studies should use other uncontrolled factors, such as cardiovascular diseases, diabetes, and stroke, to explain the relationship between SBP and AD.

KEYWORDS

Alzheimer's disease, blood pressure, systo-diastolic hypertension, risk factor, meta-analysis

1. Introduction

There are 55 million people affected by dementia worldwide (1). Alzheimer's disease (AD) is the most common cause of dementia, accounting for up to 75% of all dementia cases (2). The prevalence of AD increases every year in individuals between the ages of 65 and 85 years (3), and by the year 2050, the worldwide prevalence of AD will grow four-folds,

to 106.8 million (range 47.2–221.2) (4). While between the ages of 65 and 74 years, about 10% of people have AD, and in those over 85 years old, the risk increases by 50% (3). According to estimates by the World Health Organization (WHO), the projected global prevalence of AD by 2050 will increase by 110% from 2010 (5).

Alzheimer's disease is a neurological disorder of unknown cause, resulting in the death of brain cells (3). AD is the most common cause of cognitive impairment (6). AD is characterized by hallmark pathological changes such as extracellular Aβ plaques and intracellular neurofibrillary pathology, which selectively affect specific subclasses of neurons and brain circuits. While dementia is a general term, Alzheimer's disease is a specific brain disease. It is marked by symptoms of dementia that gradually get worse over time (7). Dementia is a rather broad syndrome of global cognitive decline. However, AD first affects the part of the brain associated with specific cognitive functions, such as language (aphasia), motor skills (apraxia), and perception (agnosia) (8, 9). Moreover, in AD, early symptoms often include changes in memory, thinking, and reasoning skills (10).

Some of the first symptoms that occur with AD (neuropsychiatric) are a direct cause of early institutionalization (11). In AD, there is an identity loss (12) and worsening in the physical and social areas (11), along with the progressive deterioration of basic cognitive (episodic memory, linguistic, and spatial orienting) and executive functions (inhibitory abilities and the visuospatial functions) (13). Emotional and mental health problems (e.g., delusions and hallucinations, abnormal behaviors, or physical violence and hitting) are common, cause distress to caregivers, and may be amenable to treatment (14, 15). All these symptoms affect the quality of life and activities of daily living in individuals diagnosed with this disease (15).

The most important non-modifiable risk factor for developing AD is age. Many cardiovascular risk factors increase with age, such as high blood pressure (BP), which, in turn, could affect the mechanisms that lead to impairment in the brain (16).

According to Ballard et al. (17), the development of dementia is associated with not only genetic factors but also acquired factors (i.e., hypertension) that could predict a higher risk of AD. In this study, we particularly focused on analyzing high BP as a risk factor for the development of AD (18, 19). The overall prevalence of high BP in adults is 25%, with more than 50% of those individuals over 60 years (20). Vascular risk factors like BP could change the anatomy of the human body by modifying vascular walls or causing ischemia and cerebral hypoxia, which may consequently lead to the development of AD (21). Furthermore, BP could generate dysfunction in the blood–brain barrier, which has been associated with the genesis of AD (22). Studies on the relationship between BP and AD have yielded inconsistent results, showing an association between AD and high BP, or no significant association between these variables (23–25). For example, Mielke found that systolic hypertension was associated with an increased risk of AD. However, the authors did not find an association between diastolic hypertension and AD (22).

Findings also established that the association between AD and hypertension was determined by age of onset (early-onset AD $\leq$ 65 years and late-onset AD $\geq$ 65 years). In fact, AD has been classified as presenile or early onset ($\leq$65 years) and as senile or late onset ($\geq$65 years) that tend to be sporadic and slow moving (26). However, it is still not clear in the current literature whether age moderates the relationship between BP and AD. Indeed, some researchers have indicated that elevated BP occurring in either middle age or late life may be involved in the development of AD (23, 27, 28). Also, one study concluded that high systolic BP (SBP) and diastolic BP (DBP) were related to worse cognitive function for persons aged 65–74 years. However, in older age ($\geq$75), higher SBP and DBP were related to adequate cognitive function (29).

Other studies have studied the relationship between hypertension and gender. Gillis and Sullivan (30) concluded that women are more likely to be prehypertensive than men. Furthermore, Anstey et al. (31) concluded that hypertension in middle-aged women was associated with greater cognitive impairment and AD. However, recent studies have shown that the prevalence of hypertension is higher in men before the sixth decade of life, although it increases in women after menopause (32).

Related to regions due to the high incidence of hypertension in developed countries, studies are aimed at prevention strategies (33, 34). In addition, the earlier onset and more aggressive development of AD in the young population have been identified as risk factors for hypertension in these countries (35).

The literature refers to various degrees of hypertension. This study was based on the cutoff points established by the International Society of Hypertension (ISH) (36). On the one hand, the ISH establishes the following measures for SBP: elevated (130–139 mmHg), grade 1 (140–159 mmHg), and grade 2 (160–179 mmHg). On the other hand, there are also three cutoff measurements for DBP: elevated (85–89 mmHg), grade 1 (90–99 mmHg), and grade 2 (100–109 mmHg) (36, 37). Mielke et al. (38) concluded that SBP measurements greater than 160 mmHg were associated with greater cognitive impairment in the elderly, which may lead to AD. Similarly, according to Launer et al. (23), elevated midlife SBP $>$ 160 mmHg and DBP $\geq$ 90 mmHg were particularly associated with an increased risk of AD.

Furthermore, longitudinal (39, 40) and cross-sectional (41, 42) studies have been used to identify risk factors and elucidate some characteristics of AD. To this end, we aggregated data from longitudinal and cross-sectional studies and used meta-analytic equation modeling to test for causal relationships. One major advantage of meta-analytic equations is that it allows an integration of the given data from all studies into one model

and specify models that have not been tested in the primary studies (43).

Based on the results and evidence of other articles and meta-analyses, we aimed to perform a meta-meta-analysis of longitudinal and cross-sectional studies to test the association between BP (high SBP and high DBP) and the risk of AD. We also aimed to pool findings separately from cross-sectional and longitudinal studies and assess the effect of BP on the risk of subsequent diagnosis of AD.

2. Materials and methods

2.1. Data collection

The search was restricted to meta-analyses assessing high SBP and DBP and AD. We applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (44). The literature searches were carried out in five electronic databases, including ISI Web of Science, Scopus, PubMed, Elsevier Science Direct, and Google Scholar. No publication date was set. The list of keywords was generated through a system of successive approximations: "blood pressure" and "Alzheimer's disease" and "meta-analysis." A Google Scholar search was also performed but was limited to the title. The literature search was carried out in English and Spanish.

2.2. Inclusion criteria

The procedures applied to carry out this meta-meta-analysis were as follows: (1) search and selection of meta-analyses assessing high SBP and DBP and AD and (2) selection of primary studies contained in the meta-analyses and the deletion of duplicates.

Meta-analyses and primary studies that met each of the following criteria were selected: (1) meta-analysis and primary studies that measured the relationship between hypertension (high SBP and DBP) and the risk of AD; (2) meta-analysis and primary studies reported data that allowed the estimation of a pooled effect size; (3) meta-analysis and primary studies that diagnosed AD through clinical examination, using defined diagnostic criteria, DSMV (9) and NINCDS-ADRDA (45); (4) meta-analysis and primary studies that reported the sample size; and (5) meta-analysis and primary studies written in English or Spanish.

To avoid bias in eligible studies, all abstracts were independently reviewed by two investigators (O.S. and A.P.). After excluding all irrelevant abstracts, the remaining articles were analyzed, and data precision was examined in detail. In meta-analysis where relevant data were lacking ($k = 1$), the authors were contacted to request additional data to be subsequently added to the meta-analysis. Then, duplicate reports were excluded to pool the primary studies. After all meta-analyses and primary studies were selected, a third researcher independently extracted the highlighted data (S.U.). Information on all data collected from the primary studies included in the meta-analysis is presented in the Supplementary Table 1.

2.3. Quality assessment

The qualities of the meta-analyses were independently coded by two co-authors using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) tool (46), which has been shown to have a good inter-rater agreement, reliability, and content validity (46, 47). Total scores for the meta-analyses were calculated as the sum of the 11 items on a binary scale. Quality classifications were set as low quality (0–4), moderate quality (5–8), and high quality (9–11).

2.4. Statistical analysis

Initially, we reported the associations between hypertension and AD for each primary study included in the previous meta-analysis (see Supplementary material).

Then, for this review of meta-analyses, first, we calculated the cumulative incidence ratio [or log risk ratio (LnRR)] of AD for both SBP and DBP for each primary study. Second, we identified separate effect sizes for SBP and DBP measurements and their relationships with the risk of AD. Third, study outcomes were grouped according to the definition of BP (SBP or DBP) and the measurement of hypertension established by the ISH: (1) SBP: elevated (130–139 mmHg), grade 1 (140–159 mmHg), and grade 2 (160–179 mmHg), and (2) DBP: elevated (85–89 mmHg), grade 1 (90–99 mmHg), and grade 2 (100–109 mmHg) (36, 37). Heterogeneity between study samples was assessed using Cochran's Q statistic (48). The I^2 statistic was calculated to express the fraction of variation between studies that was due to heterogeneity. The I^2 statistic explains the percentage of variance in the observed effects due to variance in the true effects. An I^2 value $<25\%$ was considered low heterogeneity, between 25 and 50% was considered moderate heterogeneity, and $>50\%$ was considered high heterogeneity (48). Statistical significance was set at $p \leq 0.05$. Data were analyzed using Comprehensive Meta-Analysis version 3.1 (Biostat Inc, NJ, USA) (49). Additionally, to test for the possibility of publication bias, we computed the Egger regression test. Results revealed no evidence for a publication bias (50).

For each primary study included in the meta-analysis, we calculated the following (see Table 1): (a) k or number of studies, (b) effect size, (c) 95% confidence interval (95%CI)

TABLE 1 Characteristics of the population of the AD and BP studies.

References	Variable[a]	Design[b]	*K*[c]	Regions (*N*)[d]	Sample[e]	% F[f]	Age[g]	SBP/DBP[h] measure/ mmHg	Results	Effect size[i]			AMSTAR[j] scores
										Effect size (RR)	95 % CI LLIC∼ULIC	*p*	
Lennon et al. (22)	SBP	L (13–22)	6	EU (2), NA (2), AS (2)	AD *n* = 2,208	47.3	M = 56.87	>140 mmHg	> SBP > AD	1.18	1.02–1.35	0.021	10
					HC *n* = 852,683			>160 mmHg	> SBP > AD	1.25	1.06–1.47	0.006	
								>90 mmHg	> DBP > AD[k]				
Xu et al. (51)	SBP	L (1–21)	39	EU (15), NA (20), AS (8), AF (1),	AD *n* = 21,359	50.5	M = 71.8	>140 mmHg	> SBP > AD	0.87	0.70–1.0	0.000	10
					HC *n* = 1,421,593								
	DBP		5		AD *n* = 743			>90 mmHg	> DBP = AD	1.14	0.89–1.39	0.028	
					HC *n* = 11,653								
Meng et al. (52)	SBP	L (10)	1	EU (1)	AD *n* = 79	100	*M* = 45	>140 mmHg	>SBP > AD	1.77	0.93–3.37	0.082	10
					HC *n* = 707								
Guan et al. (53)	SBP	L (2–27)	4	EU (2), NA (1), AS (1)	AD *n* = 176	56.3	40–92	>160 mmHg	>SBP and DBP =AD	1.01	0.87–1.18	0.850	9
	DBP				HC *n* = 7,283			>85 mmHg					
Wang et al. (54)	SBP	T	2	EU (1), NA (1)	AD *n* = 385	39	<65	>140 mmHg	>SBP = AD	1.50	0.56–4.04	0.036	10
					HC *n* = 3,626			>160 mmHg					
							≥65	>160 mmHg	>SBP = AD	1.00	0.79–1.25	0.180	
							65–75	>160 mmHg	>SBP = AD	1.01	0.66–1.53	0.215	
							75–85	>160 mmHg	>SBP > AD	1.07	0.63–1.82	0.052	
	DBP		2	EU (1), NA (1)	AD *n* = 385		<65	>90 mmHg	–	1.70	0.80–3.60	–	

(Continued)

10.3389/fneur.2022.1065335

TABLE 1 (Continued)

References	Variable[a]	Design[b]	*K*[c]	Regions (*N*)[d]	Sample[e]	% F[f]	Age[g]	SBP/DBP[h] measure/ mmHg	Results	Effect size[i]			AMSTAR[j] scores
										Effect size (RR)	95 % CI LLIC∼ULIC	*p*	
					HC *n* = 3626		≥65	>90 mmHg	>DBP = AD	0.75	0.43–1.32	0.066	
							65–75	>85 mmHg	>DBP = AD	0.71	0.30–1.67	0.616	
							75–85	>90 mmHg	>DBP = AD	0.52	0.32–0.85	0.267	

[a]Variable: SBP, systolic blood pressure; DBP, diastolic blood pressure.
[b]Design: T, cross-sectional; L, longitudinal.
[c]K: Number of studies.
[d]Regions: N, number of independent studies; EU, European Union; NA, North America; AS, Asia; AF, Africa.
[e]Sample: AD, participants with Alzheimer's disease; HC, health control participants.
[f]%F: percentage of women.
[g]M, mean of age.
[h]Study outcomes were grouped according to the measurement of hypertension: (1) SBP > 140 mmHg and >160 mmHg, (2) DBP > 85 mmHg and 90 mmHg [reference guides: (36, 37)].
[i]CI: 95% confidence interval; RR: risk ratio.
[j]AMSTAR, Assessing the Methodological Quality of Systematic Reviews. https://amstar.ca/Amstar_Checklist.php.
[k]Given that two studies used odds ratios and the others hazard ratios, the authors could not compute summary estimates.

of the effect, and (d) *p* (two-tailed significance) (55). We used a random-effect model for the calculation of pooled effect estimates. Then, to assess the heterogeneity of our results, subgroup analyses were performed to examine the differential effects of type of BP: (1) SBP, (2) DBP, and (3) BP (total) on the risk of AD. We did not assume a common among-study variance component across subgroups. High-resolution forest plots were also developed separately with random effects.

Additionally, moderating variables were selected based on substantive considerations and the availability of data across studies included in the meta-analysis. We anticipated interstudy heterogeneity as there was some variation between studies according to the study design (longitudinal *k effect size* = 29 vs. cross-sectional *k effect size* = 46) and the measures of SBP (>140 mmHg *k effect size* = 52 and >160 mmHg *k effect size* = 8) and DBP (>85 mmHg *k effect size* = 2 and >90 mmHg *k effect size* = 9). Finally, we also considered whether age at exposure assessment (early age of onset ≤65 *k effect size* = 39 vs. late age of onset or ≥65 *k effect size* = 36) could account for heterogeneity in associations. When possible, we used separate summary measures for early- and late-life measures of BP. Otherwise, BP in early life or late life was defined according to the mean of age. Moreover, we also analyzed the sex (male or female) in the different BP measurements. In the same line, we also analyzed the continent where the sample was recruited (Europe, Asia, and North America) in the different BP measurements.

3. Results

A total of 214 studies were identified from major databases: 61 in ISI Web of Science, 55 in Scopus, 17 in PubMed, 79 in Elsevier Science Direct, and 2 in Google Scholar. In total, 189 articles were excluded from this review for various reasons: (a) *k* = 89 were duplicates and (b) *k* = 100, in which no information was provided on the relationship between BP and AD.

A total of 25 meta-analyses were eligible for inclusion in this review of meta-analyses. Of these meta-analyses, 20 were excluded: (a) *k* = 14 studies were duplicated data; (b) *k* = 2 were systematic reviews about other issues; (c) *k* = 2 aimed to study the effect of antihypertensives on AD; and (d) *k* = 2 aimed to study genetic factors (Figure 1).

Table 1 summarizes key features of the included primary diagnosis, design, number of primary studies, regions of origin of the study, sample size, gender, mean age, results, effect sizes of the relationships between BP and AD, and AMSTAR scores. Although the meta-meta-analyses were based on the criteria established by ISH, the studies only showed values for the following cutoff points: SBP (>140 mmHg and >160 mmHg) and DBP (>85 mmHg and >90 mmHg). Eggers' test was not

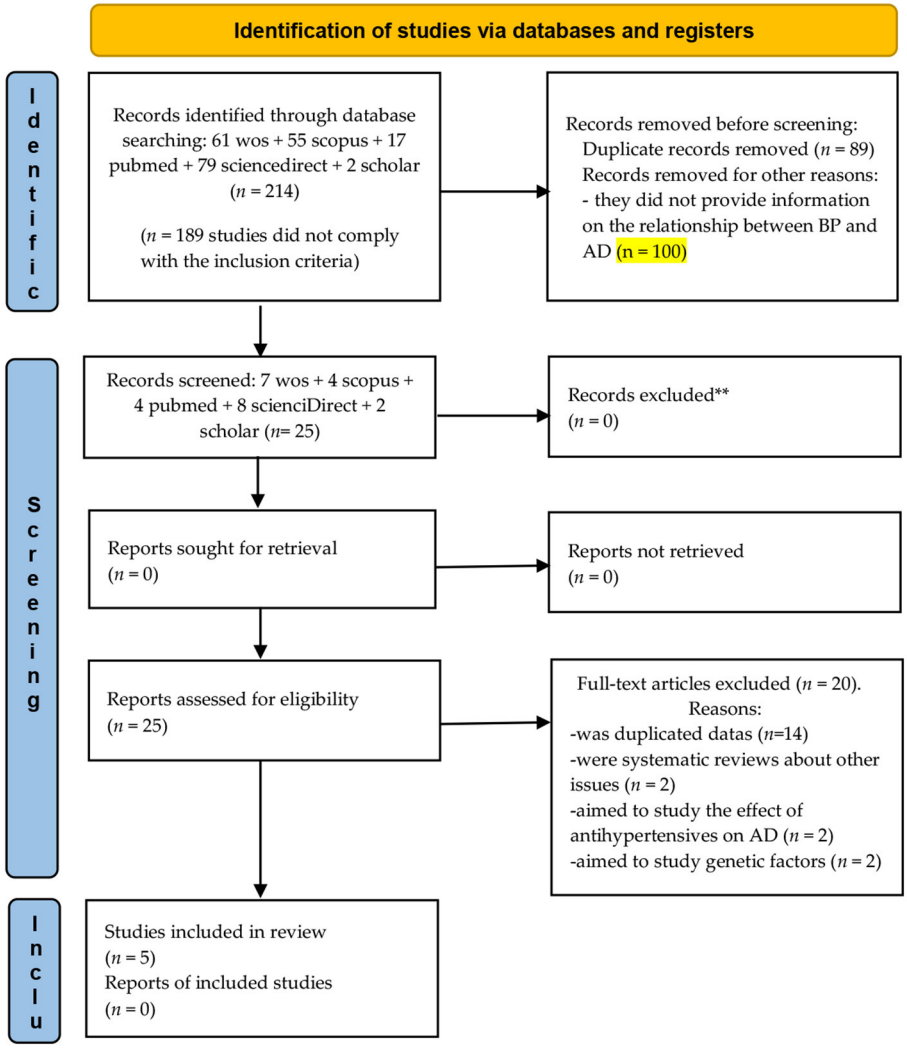

FIGURE 1
Flowchart depicting the selection of articles for our meta-analysis. From Page et al. (56).

significant: the intercept (B0) is 0.47, Se = 0.28, 95%CI (−0.09, 1.04), with $t = 1.65$, df = 73, indicating no publication bias.

3.1. BP and AD: Heterogeneity analysis

A total of 75 effect sizes were extracted from a total of five meta-analyses that included $k = 52$ primary studies. Also, 60 effect sizes provided information about high SBP and risk of AD (80%); $k = 11$ about high DBP (14.7%); and $k = 4$ about the combined effect (5.3%) (Supplementary Table 1).

For the pooling LnRR analysis, we analyzed primary studies. The total effect size was LnRR = 0.07, Se = 0.02 (0.031, 0.125), Z = 3.27, $p = 0.001$, and heterogeneity was high (Qb = 415.56, df = 74, $p = 0.0000$; $I^2 = 82.19$). These findings suggest that heterogeneity of effect may be present in some analyses.

3.2. Systolic blood pressure and AD

Four meta-analyses examined the relationship between high SBP and AD. The meta-analyses carried out by Lennon et al. (22) ($k = 11$ effect sizes; $N = 7{,}666$; $n = 1{,}520$ participants with AD and high SBP; $nHC = 6{,}146$ HC participants), Xu et al. (51) ($k = 40$ effect sizes; $N = 1{,}443{,}213$; $n = 17{,}113$ participants with AD and high SBP; $n = 1{,}426{,}100$ HC participants), Meng et al. (52) ($k = 1$ effect size; $N = 786$; $n = 79$ participants with AD and high SBP; $n = 707$ HC participants), and Wang et al. (54) ($k = 8$ effect sizes; $N = 5{,}885$; $n = 385$ participants with AD and high SBP; $n = 5{,}500$ HC participants) compared HC and AD subjects with high SBP. Only two of them (22, 52) found significant associations between high SBP and the risk of AD (Figures 2–4).

The total random effect of the high SBP value was $k = 60$ effect sizes; $N = 1{,}457{,}550$ participants; $nAD = 19{,}097$

10.3389/fneur.2022.1065335

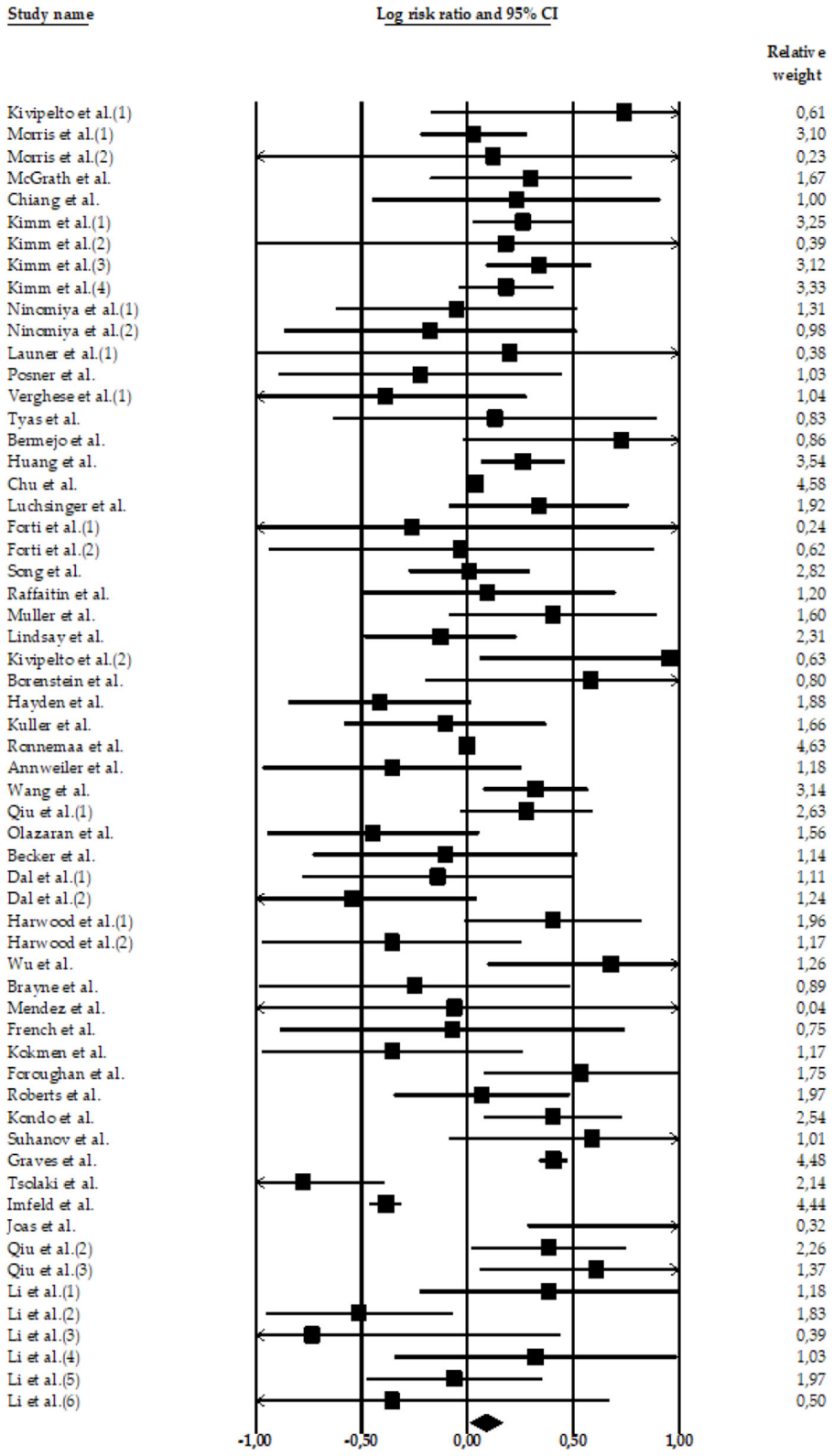

FIGURE 2
Forest plot of the meta-analysis of incidence rates of AD in participants with high SBP. Individual and pooled estimates of the association between measures of hypertension and AD. The size of the box representing the point estimate for each study in the forest plot is proportional to the contributing weight of that study estimate to the summary estimate.

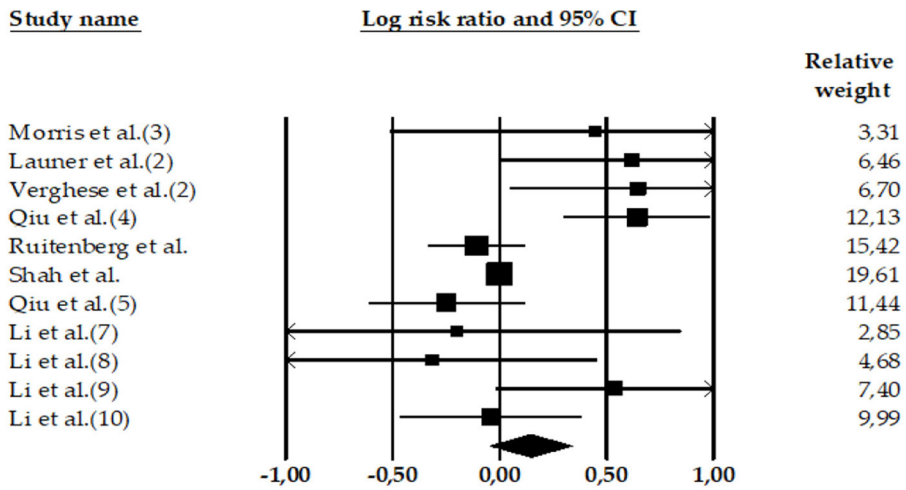

FIGURE 3
Forest plot of the meta-analysis of incidence rates of AD in participants with high DBP. Individual and pooled effect estimates of the association between DBP hypertension and AD. The size of the box representing the point estimate for each study in the forest plot is proportional to the contributing weight of that study estimate to the summary estimate.

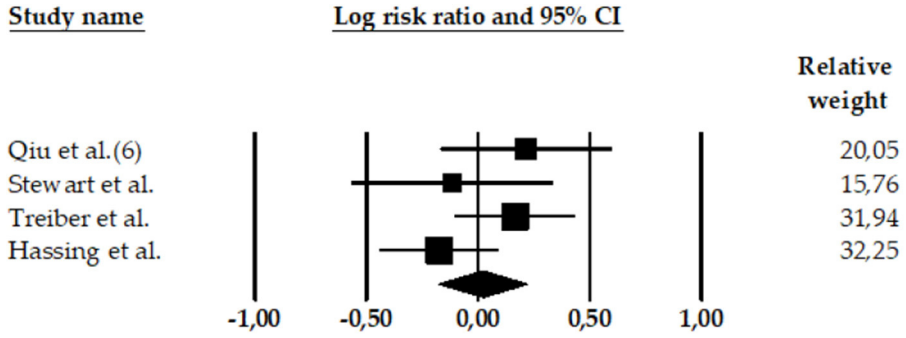

FIGURE 4
Forest plot of the meta-analysis of rates of AD in participants with high BP (high SBP and high DBP). The size of the box representing the point estimate for each study in the forest plot is proportional to the contributing weight of that study estimate to the summary estimate.

participants; *nHC* = 1,438,453 (LnRR = 0.09, 95%CI = 0.013–0.166, $Z = 2.28$, $p = 0.022$) (see Table 2). The heterogeneity was high: Q-value= 380.08, df = 59, and $I^2 = 84$.

3.3. Diastolic blood pressure and AD

Three meta-analyses showed the relationship between DBP and AD: Lennon et al. (22) ($k = 1$ effect size; $N = 378$; $n = 78$ with AD and high DBP; $n = 300$ HC participants), Xu et al. (51) ($k = 5$ effect sizes; $N = 12{,}225$; $n = 497$ with AD and high DBP; $n = 11{,}728$ HC participants), and Wang et al. (54) ($k = 5$ effect sizes; $N = 7{,}745$; $n = 306$ with AD and high DBP; $n = 7{,}439$ HC participants). None of the three meta-analyses show significant associations between high DBP and AD.

Consistently, our results ($k = 11$ effect sizes; $N = 20{,}348$; *nAD* = 881; HC = 19,467) did not find an association between high DBP and the risk of AD (LnRR = 0.15, 95% CI = −0.045 to 0.338, $Z = 1.50$, $p = 0.133$) (see Table 3). The heterogeneity was high: Q-value = 29.99, df = 10, and $I^2 = 66.65$.

3.4. High SBP and high DBP studies: Combined effect sizes

A meta-analysis reported a combined effect size for high SBP and high DBP (97). This study ($k = 4$ effect sizes; $N = 7{,}494$; $n = 211$ with AD and high SBP/DBP; $n = 7{,}283$ HC participants) found a non-significant association between high SBP and high DBP and AD (LnRR = 0.02, 95% CI = −0.179 to 0.222, Z =

TABLE 2 Individual and pooled estimates of the association between high SBP and AD.

References	Sample	Statistics for each study						
		LnRR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*
Lennon et al. (22)								
Kivipelto et al. (1) (18)	AD $n = 48$	0.74	0.47	0.22	−0.174	1.658	1.59	0.113
	HC $n = 1,400$							
Morris et al. (1) (25)	AD $n = 324$	0.03	0.13	0.02	−0.221	0.280	0.23	0.817
	HC $n = 378$							
Morris et al. (2) (25)[a]	AD $n = 54$	0.12	0.79	0.63	−1.430	1.674	0.15	0.877
	HC $n = 378$							
McGrath et al. (57)	AD $n = 81$	0.30	0.24	0.06	−0.174	0.775	1.24	0.215
	HC $n = 1,440$							
Chiang et al. (58)	AD $n = 64$	0.23	0.35	0.12	−0.448	0.910	0.67	0.505
	HC $n = 292$							
Kimm et al. (1) (59)	AD $n = 282$	0.26	0.12	0.01	0.030	0.495	2.21	0.027
	HC $n = 821$							
Kimm et al. (2) (59)	AD $n = 164$	0.18	0.60	0.36	−1.000	1.364	0.30	0.762
	HC $n = 821$							
Kimm et al. (3) (59)[a]	AD $n = 274$	0.34	0.13	0.02	0.088	0.584	2.66	0.008
	HC $n = 821$							
Kimm et al. (4) (59)[a]	AD $n = 206$	0.18	0.11	0.01	−0.041	0.405	1.60	0.109
	HC $n = 821$							
Ninomiya et al. (1) (60)	AD $n = 6$	−0.05	0.29	0.08	−0.619	0.516	−0.18	0.859
	HC $n = 149$							
Ninomiya et al. (2) (60)[a]	AD $n = 17$	−0.17	0.35	0.12	−0.865	0.516	−0.50	0.621
	HC $n = 177$							
Total (22)		**0.20**	**0.06**	**0.00**	**0.090**	**0.307**	**3.58**	**0.000**
Xu et al. (51)								
Launer et al. (1) (27)	AD $n = 81$	0.20	0.61	0.37	−0.996	1.394	0.33	0.744
	HC $n = 2.137$							
Posner et al. (24)	AD $n = 257$	−0.22	0.34	0.12	−0.892	0.446	−0.65	0.513
	HC $n = 1.259$							
Verghese et al. (1) (61)	AD $n = 65$	−0.39	0.34	0.11	−1.049	0.278	−1.14	0.255
	HC $n = 406$							
Tyas et al. (39)	AD $n = 35$	0.13	0.39	0.15	−0.634	0.897	0.34	0.737
	HC $n = 685$							

(Continued)

TABLE 2 (Continued)

References	Sample	Statistics for each study						
		LnRR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*
Bermejo et al. (62)	AD $n = 113$	0.73	0.38	0.15	−0.020	1.475	1.91	0.056
	HC $n = 3.824$							
Huang et al. (63)	AD $n = 612$	0.26	0.10	0.01	0.064	0.460	2.60	0.009
	HC $n =$ 142.744							
Chu et al. (64)	AD $n = 10$	0.04	0.02	0.00	0.009	0.069	2.54	0.011
	HC $n = 153$							
Luchsinger et al. (65)	AD $n = 246$	0.34	0.22	0.05	−0.087	0.760	1.56	0.120
	HC $n = 1.138$							
Forti et al. (1) (66)	AD $n = 18$	−0.26	0.77	0.60	−1.777	1.254	−0.34	0.735
	HC $n = 466$							
Forti et al. (2) (66)	AD $n = 30$	−0.03	0.46	0.21	−0.939	0.878	−0.07	0.948
	HC $n = 238$							
Song et al. (67)	AD $n = 416$	0.01	0.15	0.02	−0.276	0.296	0.07	0.946
	HC $n = 2.790$							
Raffaitin et al. (68)	AD $n = 134$	0.10	0.31	0.10	−0.509	0.700	0.31	0.757
	HC $n = 7.087$							
Muller et al. (69)	AD $n = 147$	0.41	0.25	0.06	−0.085	0.896	1.62	0.105
	HC $n = 1833$							
Lindsay et al. (70)	AD $n = 194$	−0.13	0.18	0.03	−0.486	0.231	−0.70	0.485
	HC $n = 4.088$							
Kivipelto et al. (1) (71)	AD $n = 48$	0.96	0.46	0.21	0.060	1.851	2.09	0.037
	HC $n = 1.449$							
Borenstein et al. (72)	AD $n = 90$	0.58	0.40	0.16	−0.196	1.361	1.47	0.143
	HC $n = 1.859$							
Hayden et al. (73)	AD $n = 104$	−0.42	0.22	0.05	−0.847	0.016	−1.89	0.059
	HC $n = 3.264$							
Kuller et al. (74)	AD $n = 330$	−0.11	0.24	0.06	−0.582	0.372	−0.43	0.665
	HC $n = 2.807$							
Ronnemaa et al. (75)	AD $n = 127$	0.00	0.09	0.01	−0.182	0.182	0.00	1.000
	HC $n = 2.268$							
Annweiler et al. (76)	AD $n = 70$	−0.36	0.31	0.10	−0.968	0.254	−1.14	0.253
	HC $n = 498$							
Wang et al. (77)	AD $n = 8.488$	0.32	0.13	0.02	0.076	0.568	2.57	0.010
	HC $n =$ 1.230.400							

(Continued)

TABLE 2 (Continued)

References		Statistics for each study						
	Sample	*LnRR*	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*
Qiu et al. (1) (78)	AD $n = 333$	0.28	0.16	0.03	−0.034	0.590	1.74	0.081
	HC $n = 1.301$							
Olazaran et al. (79)	AD $n = 68$	−0.45	0.26	0.07	−0.946	0.054	−1.75	0.080
	HC $n = 1.376$							
Becker et al. (80)	AD $n = 48$	−0.11	0.32	0.10	−0.729	0.518	−0.33	0.740
	HC $n = 288$							
Dal et al. (1) (81)	AD $n = 40$	−0.14	0.32	0.11	−0.775	0.496	−0.43	0.668
	HC $n = 576$							
Dal et al. (2) (81)	AD $n = 67$	−0.54	0.30	0.09	−1.134	0.045	−1.81	0.070
	HC $n = 781$							
Harwood et al. (1) (82)	AD $n = 202$	0.41	0.21	0.05	−0.011	0.822	1.91	0.056
	HC $n = 392$							
Harwood et al. (2) (82)	AD $n = 188$	−0.36	0.31	0.10	−0.969	0.256	−1.14	0.254
	HC $n = 84$							
Wu et al. (83)	AD $n = 201$	0.68	0.30	0.09	0.095	1.261	2.28	0.023
	HC $n = 391$							
Brayne et al. (84)	AD $n = 18$	−0.25	0.37	0.14	−0.983	0.486	−0.66	0.507
	HC $n = 340$							
Mendez et al. (85)	AD $n = 50$	−0.06	2.02	4.07	−4.015	3.891	−0.03	0.976
	HC $n = 407$							
French et al. (86)	AD $n = 76$	−0.07	0.42	0.17	−0.887	0.742	−0.17	0.861
	HC $n = 102$							
Kokmen et al. (87)	AD $n = 203$	−0.36	0.31	0.10	−0.972	0.258	−1.14	0.256
	HC $n = 415$							
Foroughan et al. (88)	AD $n = 42$	0.54	0.23	0.05	0.078	0.995	2.30	0.022
	HC $n = 115$							
Roberts et al. (89)	AD $n = 151$	0.07	0.21	0.04	−0.348	0.483	0.32	0.750
	HC $n = 264$							
Kondo et al. (90)	AD $n = 60$	0.41	0.16	0.03	0.082	0.729	2.46	0.014
	HC $n = 120$							
Suhanov et al. (91)	AD $n = 127$	0.59	0.34	0.12	−0.086	1.262	1.71	0.087
	HC $n = 260$							
Graves et al. (92)	AD $n = 18$	0.43	0.03	0.01	0.339	0.472	11.90	0.000
	HC $n = 340$							
Tsolaki et al. (93)	AD $n = 65$	−0.77	0.19	3.86	−1.161	−0.391	−3.94	7.829
	HC $n = 69$							

(Continued)

10.3389/fneur.2022.1065335

TABLE 2 (Continued)

References		Statistics for each study						
	Sample	*LnRR*	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*
Imfeld et al. (94)	AD $n = 3.541$	−0.38	3.75	1.41	−0.459	−0.312	−10.26	0.000
	HC $n = 7.086$							
Total (52)		**0.05**	**0.05**	**0.00**	**−0.038**	**0.146**	**1.16**	**0.246**
Meng et al. (52)								
Joas et al. (95)	AD $n = 79$	1.59	0.67	0.45	0.285	2.902	2.39	0.017
	HC $n = 707$							
Wang et al. (54)								
Qiu et al. (2) (96)	AD $n = 150$	0.61	0.28	0.08	0.060	1.159	2.18	0.030
	HC $n = 1.270$							
Qiu et al. (3) (96)[a]	AD $n = 124$	0.39	0.19	0.03	0.019	0.751	2.06	0.039
	HC $n = 441$							
Li et al. (1) (97)	AD $n = 14$	0.39	0.31	0.10	−0.225	0.995	1.24	0.216
	HC $n = 530$							
Li et al. (2) (97)	AD $n = 19$	−0.51	0.23	0.05	−0.953	−0.069	−2.26	0.024
	HC $n = 733$							
Li et al. (3) (97)	AD $n = 37$	−0.73	0.60	0.36	−1.908	0.440	−1.23	0.220
	HC $n = 530$							
Li et al. (4) (97)[a]	AD $n = 31$	0.32	0.34	0.12	−0.346	0.990	0.95	0.345
	HC $n = 733$							
Li et al. (5) (97)[a]	AD $n = 4$	−0.06	0.21	0.04	−0.476	0.352	−0.29	0.770
	HC $n = 733$							
Li et al. (6) (97)[a]	AD $n = 6$	−0.36	0.52	0.27	−1.384	0.670	−0.68	0.496
	HC $n = 530$							
Total (55)		**0.08**	**0.16**	**0.03**	**−0.241**	**0.399**	**0.48**	**0.629**
Total random		**0.09**	**0.04**	**0.00**	**0.013**	**0.166**	**2.28**	**0.022**

[a]Measures SBP > 160.

0.21, $p = 0.835$) (see Table 4). The heterogeneity was medium: Q-value = 4.52, df = 3, and $I^2 = 33.69$.

3.5. Subgroup analyses

Results of the subgroup analysis on the primary outcomes are presented in Table 5. Study outcomes were grouped by definition of hypertension and measures of BP (e.g., SBP, DBP, or total BP). Notably, 60 effect sizes examined SBP at both grades (22): 52 effect sizes examined only grade 1 (>140 mmHg) (51, 54) and 8 effect sizes examined only grade 2 (>160 mmHg) (53). Eleven effect sizes examined DBP at both grades: 2 effect sizes examined DBP using a cutoff point of >85 mmHg (51, 54) and 9 effect sizes >90 mmHg. Four effect sizes combined both types of hypertension (53). Moderator analyses were performed comparing effect sizes according to sex (men and women), age (≤65 and ≥66), study design (cross-sectional or C and longitudinal or L), and regions (Europe, Asia, and North America).

The results of pooling studies that reported RRs for a total score of BP showed that sex, age, and design did not moderate the relationship between hypertension and AD risk (Qb: $p \leq 0.50$). These results indicate that the risk of AD in participants with hypertension did not change significantly according to sex, age, and study design groups. However, it can be observed that there are significant relationships between different categories of the variables such as sex, age, study design, and AD (*Z*: $p \leq 0.50$). Findings revealed a significant relationship only between being women and a greater risk of AD ($p = 0.008$). Age was

TABLE 3 Individual and pooled estimates of the association between high DBP and AD.

References	*Sample*	Statistics for each study						
		LnRR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*
Lennon et al. (22)								
Morris et al. (3) (25)	AD $n = 78$	0.44	0.49	0.24	−0.513	1.402	0.91	0.363
	HC $n = 300$							
Xu et al. (51)								
Launer et al. (2) (27)	AD $n = 87$	0.62	0.31	0.10	0.005	1.236	1.98	0.048
	HC $n = 2.137$							
Verghese et al. (2) (61)	AD $n = 65$	0.65	0.31	0.09	0.048	1.246	2.12	0.034
	HC $n = 406$							
Qiu et al. (4) (78)	AD $n = 87$	0.64	0.17	0.03	0.303	0.981	3.71	0.000
	HC $n = 1.301$							
Ruitenberg et al. (98)	AD $n = 107$	−0.11	0.11	0.01	−0.331	0.120	−0.92	0.359
	HC $n = 6.985$							
Shah et al. (99)	AD $n = 151$	0.00	0.01	0.00	−0.010	0.010	0.00	1.000
	HC $n = 899$							
Total (52)		**0.27**	**0.15**	**0.02**	**−0.019**	**0.554**	**1.83**	**0.068**
Wang et al. (54)								
Qiu et al. (5) (96)	AD $n = 245$	−0.25	0.19	0.03	−0.613	0.116	−1.34	0.182
	HC $n = 2,249$							
Li et al. (7) (97)	AD $n = 22$	−0.20	0.53	0.28	−1.245	0.848	−0.37	0.710
	HC $n = 2.605$							
Li et al. (8) (97)	AD $n = 28$	−0.31	0.39	0.15	−1.086	0.457	−0.80	0.424
	HC $n = 1.321$							
Li et al. (9) (97)[a]	AD $n = 4$	0.54	0.28	0.08	−0.018	1.091	1.90	0.058
	HC $n = 905$							
Li et al. (10) (97)[a]	AD $n = 7$	−0.04	0.22	0.05	−0.464	0.383	−0.19	0.850
	HC $n = 359$							
Total (54)		−0.04	0.15	0.02	−0.339	0.263	−0.25	0.805
Total random		**0.15**	**0.10**	**0.01**	**−0.045**	**0.338**	**1.50**	**0.133**

[a]Measures DBP > 90.

also associated with increased risk of AD in early ($p = 0.008$) and late ($p = 0.047$) age of onset, and this association was also significant in cross-sectional ($p = 0.021$) and longitudinal ($p = 0.013$) studies. Regions moderated the association between BP and AD. The risk of AD was greater in studies that used samples from Asia and North America than those performed in Europe.

Results did not find significant differences in the risk of AD according to the measures of SBP (>140 and >160 mmHg) and DBP (>85 and >90 mmHg). Similarly, sex, age, design, and region did not moderate the relationship between SBP and DBP and the risk of AD, except sex in the case of DBP. Results found that women showed a stronger risk of developing AD than

TABLE 4 Individual and pooled estimates of the association between high BP and AD.

References	*Sample*	Statistics for each study						
		LnRR	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*
Guan et al. (53)								
Qiu et al. (6) (19)	AD $n = 75$	0.22	0.20	0.04	−0.168	0.599	1.10	0.272
	HC $n = 719$							
Stewart et al. (100)	AD $n = 35$	−0.12	0.23	0.05	−0.566	0.333	−0.51	0.611
	HC $n = 1.778$							
Treiber et al. (101)	AD $n = 65$	0.17	0.14	0.02	−0.103	0.434	1.21	0.227
	HC $n = 3.634$							
Hassing et al. (102)	AD $n = 36$	−0.17	0.14	0.02	−0.441	0.092	−1.28	0.199
	HC $n = 1.152$							
Total random		**0.02**	**0.10**	**0.01**	**−0.179**	**0.222**	**0.21**	**0.835**

men. It is also observed that only in longitudinal studies and Asia regions, significant associations were found between SBP and AD.

According to measures of SBP (>140 and >160 mmHg), results indicated that SBP had no significant differences in effect sizes on the risk of AD at different sexes, ages, and designs. However, for SBP > 140 mmHg, there was evidence of heterogeneity between regions in RRs of AD. Asian countries showed stronger effect sizes between SBP and risk of AD than European and North American countries. Also, results found that elevated SBP (>160 mmHg) was significantly associated with AD risk in the young elderly (≤65), longitudinal studies, and in Europa and Asia.

For DBP (>85 and >90 mmHg), there was evidence of heterogeneity between the sexes. Women with elevated DBP (>90 mmHg) showed a greater risk of AD than men. Furthermore, there were no significant differences in AD risk according to age, design, and region.

Finally, age and region did not moderate the relationship between the combined effects of BP and the risk of AD.

4. Discussion

This study analyzes the association between high BP and the risk of AD. This is the first study to evaluate this relationship by identifying previous meta-analyses and analyzing primary studies worldwide. The present study summarized the information on meta-analyses of hypertension (DBP and SBP) and AD and expanded the findings from individual studies. In this study, 52 primary studies and 75 effect sizes were extracted. Furthermore, we included some moderator variables between high DBP and high SBP and AD, such as sex, age, study design, regions, and measures of SBP and DBP.

Overall, results suggest that hypertension is associated with an increased risk of AD ($RR = 1.08$, 95%CI: 1.032, 1.13, $Z = 3.273$, $p = 0.001$). It indicates that the risk of AD increases by 8% for patients with SBP.

In this study, 46 primary studies and 60 effect sizes extracted from four meta-analyses (22, 51–53) confirm the relationship between high SBP and AD ($RR = 1.09$, 95%CI: 1.013, 1.181, $Z = 2.285$, $p = 0.022$). These results indicate that participants with high SBP increase the rate risk of AD by 9% and support findings of previous studies, suggesting that there were consistent demonstrations of a relationship between SBP and the risk of developing AD. In this vein, research demonstrated that high SBP could increase the risk of AD since it could cause neurobiological alterations (deposits of beta-amyloid protein), which lead to lesions in the brain, such as cerebral atrophy, senile plaques, and neurofibrillary tangles, which could be explanatory factors of the development of AD (103, 104). Other studies also suggest that high SBP could cause brain vascular injury, leading to increased flow of blood, cerebral patency, and cerebral amyloid angiopathy which were also associated with a higher risk of AD (105–107). However, our analysis cannot underlie the pathophysiology of AD and could only define SBP as a risk factor.

The relationship between high DBP and AD was studied through $k = 8$ primary studies and eleven effect sizes (three meta-analyses) (22, 51, 54). Findings did not find a significant association between high DBP and the risk of AD. Nevertheless, according to previous studies, these results could be explained by confounding due to associations between BP and advanced disease or other unknown modifiable risk factors (108–110).

TABLE 5 Effects of sex, age, design, and regions in different types of SBP (>140 and >160 mmHg) and DBP (>85 and >90 mmHg).

Group by		Statistics for each study									
		Effect sizes	*LnRR*	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*	I^2	*Qb*
BP (all types)											
	Sex										
	Men	54	0.06	0.04	0.00	−0.023	0.140	1.407	0.159	72.01	1.867, $p = 0.172$
	Women	21	0.16	0.06	0.00	0.041	0.274	2.657	0.008	88.38	
	Age										
	≤65	36	0.09	0.03	0.00	0.024	0.160	2.645	0.008	58.70	0.280, $p = 0.596$
	≥65	39	0.07	0.03	0.00	0.001	0.132	1.984	0.047	88.11	
	Design										
	C	46	0.06	0.03	0.00	0.010	0.120	2.303	0.021	87.61	0.744, $p = 0.389$
	L	29	0.11	0.04	0.00	0.023	0.197	2.484	0.013	36.48	
	Regions										
	Europe	23	−0.05	0.03	0.00	−0.113	0.025	−1.244	0.214	87.66	20.65, $p = 0.0001$
	Asia	15	0.19	0.04	0.00	0.115	0.284	4.627	0.000	58.27	
	North America	37	0.11	0.04	0.00	0.038	0.190	2.939	0.003	62.02	
SBP											
>140		52	0.08	0.04	0.01	−0.007	0.158	1.786	0.074	86.01	0.948, $p = 0.330$
>160		8	0.19	0.11	0.01	−0.027	0.407	1.720	0.085	3.14	
	Sex										
	Men	42	0.08	0.05	0.01	−0.015	0.174	1.649	0.099	67.99	0.107, $p = 0.744$

(Continued)

10.3389/fneur.2022.1065335

TABLE 5 (Continued)

Group by		Statistics for each study									
		Effect sizes	*LnRR*	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*	I^2	*Qb*
	Women	18	0.11	0.06	0.01	−0.012	0.221	1.158	0.079	88.94	
>140	Men	35	0.06	0.05	0.01	−0.045	0.162	1.11	0.267	71.87	0.237, $p = 0.626$
	Women	17	0.09	0.06	0.00	−0.025	0.222	1.565	0.118	89.81	
>160	Men	7	0.21	0.11	0.01	−0.009	0.426	1.880	0.060	15.65	0.018, $p = 0.895$
	Women	1	0.18	0.11	0.01	−0.041	0.405	1.601	0.109	0.000	
	Age										
	≤*65*	29	0.101	0.07	0.01	−0.034	0.250	1.495	0.135	54.50	0.133, $p = 0.715$
	≥*65*	31	0.07	0.07	0.01	−0.063	0.207	1.040	0.298	90.29	
>140	≤65	25	0.08	0.08	0.01	−0.084	0.234	0.927	0.354	49.01	0.000, $p = 0.987$
	≥65	27	0.08	0.07	0.01	−0.067	0.221	1.048	0.295	91.54	
>160	≤65	4	0.26	0.10	0.01	0.070	0.455	2.667	0.008	23.26	1.854, $p = 0.173$
	≥65	4	0.01	0.17	0.03	−0.318	0.334	0.047	0.962	0.00	
	Design										
	C	41	0.06	0.05	0.01	−0.031	0.152	1.294	0.196	88.23	1.336, $p = 0.248$
	L	19	0.16	0.07	0.01	0.018	0.302	2.206	0.027	35.78	
>140	C	41	0.06	0.05	0.00	−0.032	0.152	1.290	0.198	88.23	0.517, $p = 0.472$
	L	11	0.14	0.10	0.01	−0.052	0.327	1.425	0.154	50.73	
>160	C	–	–	–	–	–	–	–	–		–
	L	8	0.21	0.07	0.01	0.065	0.356	2.834	0.005	3.14	

(Continued)

10.3389/fneur.2022.1065335

TABLE 5 (Continued)

Group by		Statistics for each study									
		Effect sizes	*LnRR*	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*	I^2	*Qb*
	Regions										
	Europe	18	0.03	0.09	0.01	−0.148	0.198	0.284	0.777	89.30	5.785, $p =$ 0.055
	Asia	14	0.27	0.09	0.01	0.095	0.436	3.044	0.002	60.41	
	North America	28	0.01	0.07	0.01	−0.130	0.152	0.156	0.876	64.11	
>140	Europe	17	0.00	0.09	0.01	−0.187	0.176	0.057	0.955	89.62	5.985, $p = 0.050$
	Asia	11	0.29	0.10	0.01	0.091	0.493	2.854	0.004	63.14	
	North America	24	0.01	0.08	0.01	−0.143	0.160	0.109	0.913	67.66	
>160	Europe	1	0.61	0.28	0.08	0.060	1.159	2.176	0.030	0.00	3.562, $p = 0.169$
	Asia	3	0.23	0.08	0.01	0.067	0.389	2.771	0.006	9.15	
	North America	4	0.01	0.17	0.03	−0.318	0.334	0.047	0.962	0.00	
DBP											
>85		2	0.21	0.24	0.06	−0.266	0.680	0.859	0.390	61.98	0.067, $p = 0.795$
>90		9	0.14	0.11	0.01	−0.081	0.358	1.236	0.217	69.65	
	Sex										
	Men	8	−0.01	0.06	0.01	−0.13	0.118	−0.109	0.913	39.20	13.37, $p = 0.0001$
	Women	3	0.62	0.15	0.03	0.307	0.927	3.897	0.0001	0.00	
>85	Men	2	0.22	0.29	0.08	−0.344	0.782	0.763	0.446	61.98	–
	Women	–	–	–	–	–	–	–	–	–	
>90	Men	6	−0.02	0.05	0.01	−0.126	0.079	−0.452	0.641	35.53	16.052, $p = 0.0001$
	Women	3	0.62	0.15	0.02	0.321	0.915	4.081	0.0001	0.00	

(Continued)

10.3389/fneur.2022.1065335

TABLE 5 (Continued)

Group by		Statistics for each study									
		Effect sizes	*LnRR*	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*	I^2	*Qb*
	Age										
	≤65	4	0.21	0.18	0.03	−0.133	0.552	1.198	0.231	85.01	0.131, $p = 0.717$
	≥65	7	0.12	0.16	0.03	−0.196	0.442	0.756	0.449	39.41	
>85	≤65	–	–	–	–	–	–	–	–	–	–
	≥65	2	0.22	0.29	0.08	−0.344	0.782	0.763	0.446	61.98	
>90	≤65	4	0.21	0.18	0.03	−0.147	0.574	1.160	0.246	85.01	0.245, $p = 0.621$
	≥65	5	0.08	0.21	0.04	−0.334	0.485	0.363	0.716	36.35	
	Design										
	C	5	0.26	0.14	0.02	−0.015	0.537	1.854	0.064	82.58	1.345, $p = 0.246$
	L	6	0.01	0.17	0.023	−0.317	0.334	0.052	0.958	28.15	
>85	C	–	–	–	–	–	–	–	–		–
	L	2	0.22	0.29	0.08	−0.344	0.782	0.763	0.446	61.98	
>90	C	5	0.26	0.14	0.02	−0.013	0.530	1.864	0.062	82.58	2.450, $p = 0.118$
	L	4	−0.15	0.21	0.05	−0.575	0.282	−0.671	0.502	0.00	
	Regions										
	Europe	3	0.12	0.19	0.04	−0.253	0.498	0.638	0.523	87.13	0.074, $p = 0.786$
	Asia	–	–	–	–	–	–	–	–	–	
	North America	8	0.19	0.15	0.02	−0.109	0.487	1.241	0.215	49.06	
>85	Europe	–	–	–	–	–	–	–	–	–	–
	Asia	–	–	–	–	–	–	–	–	–	
	North America	2	0.22	0.29	0.08	−0.344	0.782	0.763	0.446	61.98	
>90	Europa	3	0.12	0.21	0.04	−0.278	0.525	0.604	0.546	87.13	0.041, $p = 0.840$

(Continued)

10.3389/fneur.2022.1065335

TABLE 5 (Continued)

Group by		Statistics for each study									
		Effect sizes	*LnRR*	*Se*	*Ve*	*LLIC*	*ULIC*	*Z*	*p*	I^2	*Qb*
	Asia	–	–	–	–	–	–	–	–	–	
	North America	6	0.18	0.19	0.04	−0.193	0.554	0.946	0.344	53.09	
BP (combined effects)											
	Sex										
	Men	4	0.02	0.10	0.01	−0.179	0.222	0.209	0.835	33.68	–
	Women	–	–	–	–	–	–	–	–	–	
	Age										
	≤65	3	−0.05	0.12	0.02	−0.289	0.192	−0.387	0.669	27.19	0.978, $p = 0.323$
	≥65	1	0.17	0.18	0.03	−0.182	0.513	0.934	0.350	0.00	
	Design										
	C										–
	L	2	0.02	0.10	0.01	−0.179	0.222	0.209	0.835	33.69	
	Regions										
	Europe	2	−0.01	0.19	0.04	−0.383	0.383	−0.026	0.979	62.61	0.522, $p = 0.770$
	Asia	1	−0.12	0.32	0.10	−0.736	0.503	−0.368	0.713	0.00	
	North America	1	0.16	0.26	0.07	−0.339	0.670	0.643	0.520	0.00	

10.3389/fneur.2022.1065335

For instance, secondary diseases, such as obesity, cardiovascular diseases, silent infarcts, and vascular risk factors (111) or type 2 diabetes (103, 108, 109), could be closely related to the development of AD. Hence, in these cases, it is not clear if hypertension is directly related to the risk of AD or whether AD is indirectly motivated by a secondary disease (110). Finally, there was a small number of studies analyzing DBP and AD in comparison with SBP, and in consequence, it is possible that we did not have sufficient statistical power to obtain a significant pooled estimate of the association between DBP and AD.

Related to the combined BP hypertension, only a meta-analysis (53) with four independent studies and effect sizes compared the incidence of AD between subjects with and without hypertension. These studies found that high BP is not associated with an increased risk of AD. This result is contradictory to the general view on the association between risk for AD and hypertension. For example, Guan et al. (53) highlighted that AD and hypertension are independent diseases with some common etiopathogenesis, which is a risk factor in AD.

To explore the influence of other research parameters in the relationship between high SBP and high DBP with AD, we analyzed different moderators: sex, age, study design, and region. This study does not find differences in the risk of AD according to the type of measure of SBP (>140 and >160 mmHg) and DBP (>85 and >90 mmHg). Total scores reveal significant differences between men ($RR = 0.99$, 95%CI: 0.887, 1.125, $Z = -0.109$, $p = 0.913$) and women ($RR = 1.85$, 95% CI: 1.359, 2.527, $Z = 3.897$, $p = 0.001$) (rate risk of AD increases by 85%) in the relationship of high DBP and AD, but not between SBP and AD. Specifically, the data suggest that women with high DBP (>90 mmHg) had an increased risk of AD compared with men ($RR = 1.86$, 95%CI: 1.379, 2.498, $Z = 16.05$, $p = 0.001$), which increase the rate risk of AD by 86%. These results have been shown in previous studies that worked with different samples (women and men), where AD was also associated with high DBP mainly in women (107, 108). For instance, Benetos et al. (112) found that DBP in women is associated with a higher cardiac output, pulse pressure, and heart rate (HR) factors that are related to a higher risk of AD (63.8%).

Total scores of BP show that age is associated with increased risk of AD in the early and late age of onset ($RR = 1.10$, 95%CI: 1.024, 1.174, $Z = 2.645$, $p = 0.008$; $RR = 1.07$, 95%CI: 1.001, 1.141, $Z = 0.047$, $p = 0.047$), with the rate risk of AD increases by 10% and 7%. However, the age of onset (early onset ≤65 years and late onset ≥65 years) does not moderate the relationship between high SBP/DBP and AD, showing similar effect sizes for both categories. Related to the measure of BP, this study found that elevated SBP > 160 mmHg was associated with the risk of AD in the young elderly (≤65 years), but not in those ≥65 years of age. In this vein, several studies have found that hypertension has different impacts on cognitive function at different ages (19, 22, 110). Current literature indicates that hypertension is a risk factor for cognitive decline in midlife and young old age but may be protective against cognitive decline in late life (22). For example, some authors concluded that high BP at the early age of onset impacted cognitive functions and increased the risk of developing AD in older age (19, 113). Iadecola et al. (114) also found that hypertension in early onset is associated with a higher risk of AD. Therefore, changes in BP may be due to hemodynamic regulation being altered by neurodegenerative processes in the years preceding disease onset (22).

The only variable that moderates the relationship between BP and AD is the region. We observe a higher risk of AD in Asia with SBP >140 mmHg ($RR = 1.34$, 95%CI: 1.096, 1.637, $Z = 2.854$, $p = 0.004$) compared with European ($RR = 0.99$, 95%CI: 0.829, 1.193, $Z = -0.057$, $p = 0.955$) and North America ($RR = 1.01$, 95%CI: 0.866, 1.174, $Z = 0.109$, $p = 0.913$). Therefore, the rate risk of AD in Asia increases by 34%. These results are related to the findings of some studies. During the past four decades, the highest BP measurements worldwide have shifted from high-income countries to low-income countries, such as South Asia and Africa (115), which could explain our results (116, 117). On the one hand, several authors suggest that recent lifestyle changes in Asia countries, such as diet, changing demographics, urbanization, environmental interactions, and other factors, may help explain this relationship (117). On the other hand, one study with data from 90 countries showed that the percentage of people with hypertension receiving treatment increased in both high-income and low- and middle-income countries, but the gap between them widened (118). Moreover, our results also show that the risk of AD related to SBP > 160 mmHg in Europe ($RR = 0.61$, 95%CI: 0.060, 1.159, $Z = 2.176$, $p = 0.030$) and Asia ($RR = 0.23$, 95%CI: 0.067, 0.389, $Z = 2.771$, $p = 0.006$) is significant. However, North America ($RR = 0.01$, 95%CI: −0.318, 0.334, $Z = 0.047$, $p = 0.962$) did not find a significant relationship. Despite these results, the strength of the association between SBP (>160 mmHg) and AD risk is similar in the three regions.

Finally, results do not find differences in the effect size of the association between high SBP and DBP and the risk of AD according to the type of design (cross-sectional and longitudinal). Our results found an association between BP and the risk of AD in both types of studies. However, findings confirm that the relationship between higher SBP and AD is only significant in longitudinal studies and with SBP > 160 mmHg ($RR = 1.23$, 95%CI: 1.067, 1.428, $Z = 2.834$, $p = 0.005$), so the rate risk of AD increases by 23%, while high DBP (>85 and >90 mmHg) is not related to increased AD risk. In this vein, previous work found differences according to the type of design that may result in part from the use of different definitions of hypertension and non-uniform measures of high or low BP. In this study, we use standardized criteria to define BP (SBP > 140/160 mmHg and DBP > 85/90 mmHg) and AD (clinical criteria) which could explain that there are no differences according to the study design. After controlling

for this confounding factor, the effect size of longitudinal studies is higher in all the BP and SBP measures, although the differences do not reach significance. Longitudinal studies provide an opportunity to assess the temporal relationship between BP and AD and the length of follow-up remains relevant since hypertension could render individuals more vulnerable to comorbid conditions, such as cerebrovascular disease, that confer greater risk for AD during long periods of follow-up.

However, there are some limitations to our study. The key limitation is that only a small number of studies examined the association between DBP, both types of BP combined, and AD compromising the generalizability of the results. Furthermore, it is likely that due to the procedure used in this meta-meta-analysis, some primary studies were not included. Another challenge was that studies reported outcomes using different metrics (OR, HR, and RR). Likewise, not all the cutoff points established by ISH could be analyzed since the stages of SBP $\geq$ 130–139 and DBP $\geq$ 100 could not be defined due to the lack of primary studies. Other confounders may also influence the study's findings. For example, results were not adjusted for other risk variables including cardiovascular disease, stroke, alcohol consumption, smoking, kidney disease, and many others. Also, two studies did not report the mean age of the sample, and they were not included in the moderator analysis. Moreover, the relationship between hypertension and AD could not be thought of as binary but rather as a dynamic one, changing with life stage and disease state. Hence, a single measurement of BP may not accurately reflect the participant's average BP measurements. Additionally, data on the age at the onset of hypertension and years of living with the condition may be important in clarifying temporal relationships between hypertension and AD. Also, we did not examine the potentially modifying impact of antihypertensive therapy on the relationship between hypertension and AD. In addition, another limitation is the absence of studies from South America and Australia. Finally, we did not include educational level as a moderator variable since the external validity of some of the results has been questioned. The primary studies contained in this meta-analysis used very different forms of measurement. For instance, some studies analyzed education using individual (i.e., no formal education, mandatory education, secondary studies, university studies) (79, 88) or community-based samples (i.e., family education level, region, or country) (80, 88), quantitative (linear relation between the number of years of education and the risk of dementia) (81, 83) or qualitative measures (a threshold effect at a given level of education) (86), and composite measures (i.e., socioeconomic status, SES defines education plus income) (67, 119) that show different results. Therefore, we should interpret our results cautiously.

Several strengths of our review of a meta-analysis should be emphasized. First, most prior studies were drawn from general community samples or non-AD-specific studies (vascular dementia, cortical dementia, or dementia in general), whereas the current study relied on AD. Second, we add to the current literature by analyzing 52 primary studies extracted from the previous meta-analysis increasing the statistical power of our results. Third, we analyzed the impact of different moderators (sex, age, study design, region, and measures of SBP/DBP) to explore the influence of other research parameters in the relationship between high SBP and DBP and AD. Finally, we want to focus on effect sizes since the statistical significance should never be interpreted as evidence that an effect had clinical importance. It is important to note that the effect sizes were "relatively small" and the variation is great within the same meta-analysis. Therefore, the clinical significance and practical importance of these results should be considered in relation to the patient's status, goals, and clinician experience.

As a practical implication, this study suggests that high SBP could be a risk factor for AD. There is limited evidence that single cardiovascular risk factors affect AD risk, but the strength of the association is influenced greatly by changing the parameters of the risk factors and in particular by identifying interactions between the factors. Future research should confirm this and determine whether stabilizing BP might be a target to slow or decline the development of AD.

5. Conclusion

This study analyzes the association between SBP/DBP/combined BP and the risk of developing AD. A total of five meta-analyses and 52 primary studies were analyzed in this review of meta-analysis. Our study found that SBP is associated with an increased risk of AD by 11%, although no association was found for DBP. Measures of SBP >140, SBP >160, DBP >85, and DBP >90 do not moderate the relationship between SBP and DBP and AD. Moderator analysis (sex, age, study design, region, and measures of SBP/DBP) shows a significant association between high DBP (>90) and AD in women. The age of onset (early-onset AD $\leq$65 years and late-onset AD or senile AD $\geq$65 years) did not moderate the relationship between SBP and DBP and AD. Finally, regarding the type of study, there were no differences in the association between BP and AD between longitudinal and cross-sectional studies. However, Asian countries showed stronger effect sizes between SBP > 140 and risk of AD than European and North American countries. Future work should use other uncontrolled factors (e.g., cardiovascular diseases, diabetes, and stroke) to explain the relationship between high BP and AD.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

OS-V and AP-M conceived and designed the analysis, collected the data, contributed data or analysis tools, performed analysis, and wrote the paper. JP-B wrote the paper. SU-L contributed data or analysis tools, performed analysis, and wrote the paper. All authors take full responsibility for the data, the analyses and interpretation, and the conduct of the research, full access to all of the data and the right to publish any and all data. All authors contributed to the article and approved the submitted version.

Funding

This study was partially funded by grant Y133GI awarded by the University of Burgos (Spain) to the Social Inclusion and Quality of Life (SIQoL) research group. This work was partially supported by FEDER funds and the Spanish State Research Agency (Projects PID2019-104263RB-C44 and PDC2021-121021-C22) and the Regional Government of "Castilla y León" and FEDER funds (Project BU056P20).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1065335/full#supplementary-material

References

1. Han H-F, Yen H-C, Wu H-C, Tan H-Y, Xu W, Jiang H-S, et al. Ultrasensitive detection of Alzheimer's amyloids on a plasmonic-gold platform. *ACS Appl Mater Interfaces.* (2021) 13:57036–42. doi: 10.1021/acsami.1c19157

2. Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues Clin Neurosci.* (2009) 11:111–28. doi: 10.31887/DCNS.2009.11.2/cqiu

3. Bhushan I, Kour M, Kour G, Gupta S, Sharma S, Yadav A. Alzheimer's disease: causes and treatment—a review. *Ann Biotechnol.* (2018) 1:1002. doi: 10.33582/2637-4927/1002

4. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement.* (2007) 3:186–91. doi: 10.1016/j.jalz.2007.04.381

5. Satizabal CL, Beiser AS, Chouraki V, Chêne G, Dufouil C, Seshadri S. Incidence of dementia over three decades in the Framingham Heart Study. *N Engl J Med.* (2016) 374:523–32. doi: 10.1056/NEJMoa1504327

6. Gottesman RT, Stern Y. Behavioral and psychiatric symptoms of dementia and rate of decline in Alzheimer's disease. *Front Pharmacol.* (2019) 10:1062. doi: 10.3389/fphar.2019.01062

7. Vickers JC, Mitew S, Woodhouse A, Fernandez-Martos C, Kirkcaldie MT, Canty AJ, et al. Defining the earliest pathological changes of Alzheimer's disease. *Curr Alzheimer Res.* (2016) 13:281–7. doi: 10.2174/1567205013666151218150322

8. Reisberg B, Jamil IA, Khan S, Monteiro I, Torossian C, Ferris S, et al. Staging dementia. *Princ Pract Geriatr Psychiatry.* (2010) 31:162–9. doi: 10.1002/9780470669600.ch31

9. American Psychiatric Association (APA). *Diagnosis and Statistical Manual of Mental Disorders Fifth Edition, Text Revision (DSM-5-TR).* (2022). Washington, DC: APA. doi: 10.1176/appi.books.9780890425787

10. Groves WC, Brandt J, Steinberg M, Warren A, Rosenblatt A, Baker A, et al. Vascular dementia and Alzheimer's disease: is there a difference? *J Neuropsychiatry Clin Neurosci.* (2000) 12:305–15. doi: 10.1176/jnp.12.3.305

11. Epperly TD, Dunay MA, Boice JL. Alzheimer disease: pharmacologic and nonpharmacologic therapies for cognitive and functional symptoms. *Am Fam Physician.* (2017) 95:771–8.

12. Orona CJ. Temporality and identity loss due to Alzheimer's disease. *Soc Sci Med.* (1990) 30:1247–56. doi: 10.1016/0277-9536(90)90265-T

13. Guarino A, Favieri F, Boncompagni I, Agostini F, Cantone M, Casagrande M. Executive functions in Alzheimer disease: a systematic review. *Front Aging Neurosci.* (2019) 10:437. doi: 10.3389/fnagi.2018.00437

14. Deutsch LH, Bylsma FW, Rovner BW, Steele C, Folstein MF. Psychosis and physical aggression in probable Alzheimer's disease. *Am J Psychiatry* (1991) 148, 1159–63. doi: 10.1176/ajp.148.9.1159

15. Giebel CM, Sutcliffe C, Challis D. Activities of daily living and quality of life across different stages of dementia: a UK study. *Aging Ment Health.* (2015) 19:63–71. doi: 10.1080/13607863.2014.915920

16. Castelli WP, Wilson PWF, Levy D, Anderson K. Cardiovascular risk factors in the elderly. *Am J Cardiol.* (1989) 63:12–9. doi: 10.1016/0002-9149(89)90110-0

17. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Enfermedad de Alzheimer. *Lancet.* (2011) 377:1019–31. doi: 10.1016/S0140-6736(10)61349-9

18. Kivipelto M, Helkala E-L, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ.* (2001) 322:1447–51. doi: 10.1136/bmj.322.7300.1447

19. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol.* (2005) 4:487–99. doi: 10.1016/S1474-4422(05)70141-1

20. Marfany A, Sierra C, Camafort M, Domenech M, Coca A. High blood pressure, Alzheimer disease and antihypertensive treatment. *Panminerva Med.* (2018) 60:8–16. doi: 10.23736/S0031-0808.18.03360-8

21. Silva JAD. *Caracterização das abordagens farmacológicas usadas no tratamento das demências-análise de casos do CHCB (Doctoral dissertation)* (2014).

22. Lennon MJ, Makkar SR, Crawford JD, Sachdev PS. Midlife hypertension and Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis.* (2019) 71:307–16. doi: 10.3233/JAD-190474

23. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study? *Neurobiol Aging.* (2000) 21:49–55. doi: 10.1016/S0197-4580(00)00096-8

24. Posner HB, Tang M-X, Luchsinger J, Lantigua R, Stern Y, Mayeux R. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. *Neurology.* (2002) 58:1175–81. doi: 10.1212/WNL.58.8.1175

25. Morris MC, Scherr PA, Hebert LE, Glynn RJ, Bennett DA, Evans DA. Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. *Arch Neurol.* (2001) 58:1640–6. doi: 10.1001/archneur.58.10.1640

26. Miyoshi K. What is 'early onset dementia'? *Psychogeriatrics.* (2009) 9:67–72. doi: 10.1111/j.1479-8301.2009.00274.x

27. Launer L, White L, Petrovitch H, Ross G, Curb J. Cholesterol and neuropathologic markers of AD: a population-based autopsy study. *Neurology.* (2001) 57:1447–52. doi: 10.1212/WNL.57.8.1447

28. Guo Z, Viitanen M, Fratiglioni L, Winblad B. Low blood pressure and dementia in elderly people: the Kungsholmen project. *BMJ.* (1996) 312:805–8. doi: 10.1136/bmj.312.7034.805

29. Euser SM, Van Bemmel T, Schram MT, Gussekloo J, Hofman A, Westendorp RG, et al. The effect of age on the association between blood pressure and cognitive function later in life. *J Am Geriatr Soc.* (2009) 57:1232–7. doi: 10.1111/j.1532-5415.2009.02264.x

30. Gillis EE, Sullivan JC. Sex differences in hypertension: recent advances. *Hypertension.* (2016) 68:1322–7. doi: 10.1161/HYPERTENSIONAHA.116.06602

31. Anstey KJ, Peters R, Mortby ME, Kiely KM, Eramudugolla R, Cherbuin N, et al. Association of sex differences in dementia risk factors with sex differences in memory decline in a population-based cohort spanning 20-76 years. *Sci Rep.* (2021) 11:7710. doi: 10.1038/s41598-021-86397-7

32. Ramirez LA, Sullivan JC. Sex differences in hypertension: where we have been and where we are going. *Am J Hypertens.* (2018) 31:1247–54. doi: 10.1093/ajh/hpy148

33. Zhou B, Danaei G, Stevens GA, Bixby H, Taddei C, Carrillo-Larco RM, et al. Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. *Lancet.* (2019) 394:639–51. doi: 10.1016/S0140-6736(19)31145-6

34. Mills KT, Obst KM, Shen W, Molina S, Zhang H-J, He H, et al. Comparative effectiveness of implementation strategies for blood pressure control in hypertensive patients: a systematic review and meta-analysis. *Ann Intern Med.* (2018) 168:110–20. doi: 10.7326/M17-1805

35. Tibazarwa KB, Damasceno AA. Hypertension in developing countries. *Can J Cardiol.* (2014) 30:527–33. doi: 10.1016/j.cjca.2014.02.020

36. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International society of hypertension global hypertension practice guidelines. *Hypertension.* (2020) 75:1334–57. doi: 10.1161/HYPERTENSIONAHA.120.15026

37. Stergiou GS, Parati G, McManus RJ, Head GA, Myers MG, Whelton PK. Guidelines for blood pressure measurement: development over 30 years. *J Clin Hypertens.* (2018) 20:1089–91. doi: 10.1111/jch.13295

38. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. *Clin Epidemiol.* (2014) 6:37. doi: 10.2147/CLEP.S37929

39. Tyas SL, Manfreda J, Strain LA, Montgomery PR. Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. *Int J Epidemiol.* (2001) 30:590–7. doi: 10.1093/ije/30.3.590

40. Gao Y, Huang C, Zhao K, Ma L, Qiu X, Zhang L, et al. Retracted: Depression as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Int J Geriatr Psychiatry.* (2013) 28:441–9. doi: 10.1002/gps.3845

41. Prins N, Den Heijer T, Hofman A, Koudstaal P, Jolles J, Clarke R, et al. Homocysteine and cognitive function in the elderly: the Rotterdam Scan Study. *Neurology.* (2002) 59:1375–80. doi: 10.1212/01.WNL.0000032494.05619.93

42. Nutaitis AC, Tharwani SD, Serra MC, Goldstein FC, Zhao L, Sher SS, et al. Diet as a risk factor for cognitive decline in African Americans and Caucasians with a parental history of Alzheimer's disease: a cross-sectional pilot study dietary patterns. *J Prev Alzheimers Dis.* (2019) 6:50–5. doi: 10.14283/jpad.2018.44

43. Lesener T, Gusy B, Wolter C. The job demands-resources model: a meta-analytic review of longitudinal studies. *Work Stress.* (2019) 33:76–103. doi: 10.1080/02678373.2018.1529065

44. Urrutia G, Bonfill X. PRISMA declaration: a proposal to improve the publication of systematic reviews and meta-analyses. *Med Clín.* (2010) 135:507–11. doi: 10.1016/j.medcli.2010.01.015

45. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology.* (1984) 34:939–939. doi: 10.1212/WNL.34.7.939

46. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol.* (2007) 7:10. doi: 10.1186/1471-2288-7-10

47. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol.* (2009) 62:1013–20. doi: 10.1016/j.jclinepi.2008.10.009

48. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. *Introduction to Meta-Analysis*. Hoboken, NJ: John Wiley and Sons (2011). p. 434.

49. Borenstein M, Hedges L, Higgins J, Rothstein H. *Comprehensive Meta-Analysis (CMA) Software* (2007).

50. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* (1997) 315:629–34. doi: 10.1136/bmj.315.7109.629

51. Xu W, Tan L, Wang H-F, Jiang T, Tan M-S, Tan L, et al. Meta-analysis of modifiable risk factors for Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* (2015) 86:1299–306. doi: 10.1136/jnnp-2015-310548

52. Meng X-F, Yu J-T, Wang H-F, Tan M-S, Wang C, Tan C-C, et al. Midlife vascular risk factors and the risk of Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis.* (2014) 42:1295–310. doi: 10.3233/JAD-140954

53. Guan J-W, Huang C-Q, Li Y-H, Wan C-M, You C, Wang Z-R, et al. No association between hypertension and risk for Alzheimer's disease: a meta-analysis of longitudinal studies. *J Alzheimers Dis.* (2011) 27:799–807. doi: 10.3233/JAD-2011-111160

54. Wang Z-T, Xu W, Wang H-F, Tan L, Tan C-C, Li J-Q, et al. Blood pressure and the risk of dementia: a dose-response meta-analysis of prospective studies. *Curr Neurovasc Res.* (2018) 15:345–58. doi: 10.2174/1567202616666181128114523

55. Lipsey MW, Wilson DB. *Practical Meta-Analysis.* London: SAGE publications, Inc. (2001).

56. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (2021) 372:n71. doi: 10.1136/bmj.n71

57. McGrath ER, Beiser AS, DeCarli C, Plourde KL, Vasan RS, Greenberg SM, et al. Blood pressure from mid-to late life and risk of incident dementia. *Neurology.* (2017) 89:2447–54. doi: 10.1212/WNL.0000000000004741

58. Chiang C-J, Yip P-K, Wu S-C, Lu C-S, Liou C-W, Liu H-C, et al. Midlife risk factors for subtypes of dementia: a nested case-control study in Taiwan. *Am J Geriatr Psychiatry.* (2007) 15:762–71. doi: 10.1097/JGP.0b013e318050c98f

59. Kimm H, Lee P, Shin Y, Park K, Jo J, Lee Y, et al. Mid-life and late-life vascular risk factors and dementia in Korean men and women. *Arch Gerontol Geriatr.* (2011) 52:e117–22. doi: 10.1016/j.archger.2010.09.004

60. Ninomiya T, Ohara T, Hirakawa Y, Yoshida D, Doi Y, Hata J, et al. Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama study. *Hypertension.* (2011) 58:22–8. doi: 10.1161/HYPERTENSIONAHA.110.163055

61. Verghese J, Lipton R, Hall C, Kuslansky G, Katz M. Low blood pressure and the risk of dementia in very old individuals. *Neurology.* (2003) 61:1667–72. doi: 10.1212/01.WNL.0000098934.18300.BE

62. Bermejo-Pareja F, Benito-León J, Louis ED, Trincado R, Carro E, Villarejo A, et al. Risk of incident dementia in drug-untreated arterial hypertension: a population-based study. *J Alzheimers Dis.* (2010) 22:949–58. doi: 10.3233/JAD-2010-101110

63. Huang C-C, Chung C-M, Leu H-B, Lin L-Y, Chiu C-C, Hsu C-Y, et al. Diabetes mellitus and the risk of Alzheimer's disease: a nationwide population-based study. *PLoS ONE.* (2014) 9:e87095. doi: 10.1371/journal.pone.0087095

64. Chu L-W, Tam S, Wong RL, Yik P-Y, Song Y, Cheung BM, et al. Bioavailable testosterone predicts a lower risk of Alzheimer's disease in older men. *J Alzheimers Dis.* (2010) 21:1335–45. doi: 10.3233/JAD-2010-100027

65. Luchsinger J, Reitz C, Honig LS, Tang M-X, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology.* (2005) 65:545–51. doi: 10.1212/01.wnl.0000172914.08967.dc

66. Forti P, Pisacane N, Rietti E, Lucicesare A, Olivelli V, Mariani E, et al. Metabolic syndrome and risk of dementia in older adults. *J Am Geriatr Soc.* (2010) 58:487–92. doi: 10.1111/j.1532-5415.2010.02731.x

67. Song X, Mitnitski A, Rockwood K. Nontraditional risk factors combine to predict Alzheimer disease and dementia. *Neurology.* (2011) 77:227–34. doi: 10.1212/WNL.0b013e318225c6bc

68. Raffaitin C, Gin H, Empana J-P, Helmer C, Berr C, Tzourio C, et al. Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: the Three-City Study. *Diabetes Care.* (2009) 32:169–74. doi: 10.2337/dc08-0272

69. Muller M, Tang M-X, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Metabolic syndrome and dementia risk in a multiethnic elderly cohort. *Dement Geriatr Cogn Disord.* (2007) 24:185–92. doi: 10.1159/000105927

70. Lindsay J, Laurin D, Verreault R, Hébert R, Helliwell B, Hill GB, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol.* (2002) 156:445–53. doi: 10.1093/aje/kwf074

71. Kivipelto M, Helkala E-L, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, et al. Apolipoprotein E ε4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. *Ann Intern Med.* (2002) 137:149–55. doi: 10.7326/0003-4819-137-3-200208060-00006

72. Borenstein AR, Wu Y, Mortimer JA, Schellenberg GD, McCormick WC, Bowen JD, et al. Developmental and vascular risk factors for Alzheimer's disease. *Neurobiol Aging.* (2005) 26:325–34. doi: 10.1016/j.neurobiolaging.2004.04.010

73. Hayden KM, Zandi PP, Lyketsos CG, Khachaturian AS, Bastian LA, Charoonruk G, et al. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. *Alzheimer Dis Assoc Disord.* (2006) 20:93–100. doi: 10.1097/01.wad.0000213814.43047.86

74. Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, et al. Risk factors for dementia in the cardiovascular health cognition study. *Neuroepidemiology.* (2003) 22:13–22. doi: 10.1159/000067109

75. Rönnemaa E, Zethelius B, Lannfelt L, Kilander L. Vascular risk factors and dementia: 40-year follow-up of a population-based cohort. *Dement Geriatr Cogn Disord.* (2011) 31:460–6. doi: 10.1159/000330020

76. Annweiler C, Rolland Y, Schott AM, Blain H, Vellas B, Herrmann FR, et al. Higher vitamin D dietary intake is associated with lower risk of Alzheimer's disease: a 7-year follow-up. *Gerontol Ser Biomed Sci Med Sci.* (2012) 67:1205–11. doi: 10.1093/gerona/gls107

77. Wang K-C, Woung L-C, Tsai M-T, Liu C-C, Su Y-H, Li C-Y. Risk of Alzheimer's disease in relation to diabetes: a population-based cohort study. *Neuroepidemiology.* (2012) 38:237–44. doi: 10.1159/000337428

78. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. *Arch Intern Med.* (2006) 166:1003–8. doi: 10.1001/archinte.166.9.1003

79. Olazaran J, Trincado R, Bermejo-Pareja F. Cumulative effect of depression on dementia risk. *Int J Alzheimer's Dis.* (2013) 2013:457175. doi: 10.1155/2013/457175

80. Becker JT, Chang Y-F, Lopez OL, Dew MA, Sweet RA, Barnes D, et al. Depressed mood is not a risk factor for incident dementia in a community-based cohort. *Am J Geriatr Psychiatry.* (2009) 17:653–63. doi: 10.1097/JGP.0b013e3181aad1fe

81. Dal Forno G, Palermo MT, Donohue JE, Karagiozis H, Zonderman AB, Kawas CH. Depressive symptoms, sex, and risk for Alzheimer's disease. *Ann Neurol.* (2005) 57:381–7. doi: 10.1002/ana.20405

82. Harwood DG, Barker WW, Loewenstein DA, Ownby RL, George-Hyslop PS, Mullan M, et al. cross-ethnic analysis of risk factors for AD in white Hispanics and white non-Hispanics. *Neurology.* (1999) 52:551–551. doi: 10.1212/WNL.52.3.551

83. Wu C, Zhou D, Wen C, Zhang L, Como P, Qiao Y. Relationship between blood pressure and Alzheimer's disease in Linxian County, China. *Life Sci.* (2003) 72:1125–33. doi: 10.1016/S0024-3205(02)02367-6

84. Brayne C, Gill C, Huppert FA, Barkley C, Gehlhaar E, Girling DM, et al. Vascular risks and incident dementia: results from a cohort study of the very old. *Dement Geriatr Cogn Disord.* (1998) 9:175–80. doi: 10.1159/000017043

85. Mendez MF, Underwood KL, Zander BA, Mastri AR, Sung JH, Frey WH. Risk factors in Alzheimer's disease: a clinicopathologic study. *Neurology.* (1992) 42:770–770. doi: 10.1212/WNL.42.4.770

86. French LR, Schuman LM, Mortimer JA, Hutton JT, Boatman RA, Christians B, et al. case-control study of dementia of the Alzheimer type. *Am J Epidemiol.* (1985) 121:414–21. doi: 10.1093/oxfordjournals.aje.a114013

87. Kokmen E, Beard CM, Chandra V, Offord KP, Schoenberg BS, Ballard DJ. Clinical risk factors for Alzheimer's disease: a population-based case-control study. *Neurology.* (1991) 41:1393–1393. doi: 10.1212/WNL.41.9.1393

88. Foroughan M, Farahani ZG, Shariatpanahi M, Vaezinejad M, Akbari Kamerani AA, Sheikhvatan M. Risk factors of Alzheimer's disease among Iranian population. *Curr Alzheimer Res.* (2008) 5:70–2. doi: 10.2174/156720508783884594

89. Roberts RO, Cha RH, Knopman DS, Petersen RC, Rocca WA. Postmenopausal estrogen therapy and Alzheimer disease: overall negative findings. *Alzheimer Dis Assoc Disord.* (2006) 20:141–6. doi: 10.1097/00002093-200607000-00004

90. Kondo K, Niino M, Shido K, A. Case-control study of Alzheimer's disease in Japan—significance of life-styles. *Dement Geriatr Cogn Disord.* (1994) 5:314–26. doi: 10.1159/000106741

91. Suhanov AV, Pilipenko PI, Korczyn AD, Hofman A, Voevoda MI, Shishkin SV, et al. Risk factors for Alzheimer's disease in Russia: a case-control study. *Eur J Neurol.* (2006) 13:990–5. doi: 10.1111/j.1468-1331.2006.01391.x

92. Graves AB, White E, Koepsell TD, Reifler BV, Van Belle G, Larson EB, et al. case-control study of Alzheimer's disease. *Ann Neurol Off J Am Neurol Assoc Child Neurol Soc.* (1990) 28:766–74. doi: 10.1002/ana.410280607

93. Tsolaki M, Fountoulakis K, Chantzi E, Kazis A. Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of a Greek population. *Int Psychogeriatr.* (1997) 9:327–41. doi: 10.1017/S104161029700447X

94. Imfeld P, Bodmer M, Jick SS, Meier CR. Metformin, other antidiabetic drugs, and risk of Alzheimer's disease: a population-based case-control study. *J Am Geriatr Soc.* (2012) 60:916–21. doi: 10.1111/j.1532-5415.2012.03916.x

95. Joas E, Bäckman K, Gustafson D, Östling S, Waern M, Guo X, et al. Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years. *Hypertension.* (2012) 59:796–801. doi: 10.1161/HYPERTENSIONAHA.111.182204

96. Qiu C, Xu W, Winblad B, Fratiglioni L. Vascular risk profiles for dementia and Alzheimer's disease in very old people: a population-based longitudinal study. *J Alzheimers Dis.* (2010) 20:293–300. doi: 10.3233/JAD-2010-1361

97. Li G, Rhew IC, Shofer JB, Kukull WA, Breitner JCS, Peskind E, et al. Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study. *J Am Geriatr Soc.* (2007) 55:1161–7. doi: 10.1111/j.1532-5415.2007.01233.x

98. Ruitenberg A, Skoog I, Ott A, Aevarsson O, Witteman JC, Lernfelt B, et al. Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. *Dement Geriatr Cogn Disord.* (2001) 12:33–9. doi: 10.1159/000051233

99. Shah RC, Wilson RS, Bienias JL, Arvanitakis Z, Evans DA, Bennett DA. Relation of blood pressure to risk of incident Alzheimer's disease and change in global cognitive function in older persons. *Neuroepidemiology.* (2006) 26:30–6. doi: 10.1159/000089235

100. Stewart R, Xue Q-L, Masaki K, Petrovitch H, Ross GW, White LR, et al. Change in blood pressure and incident dementia: a 32-year prospective study. *Hypertension.* (2009) 54:233–40. doi: 10.1161/HYPERTENSIONAHA.109.128744

101. Treiber KA, Lyketsos CG, Corcoran C, Steinberg M, Norton M, Green RC, et al. Vascular factors and risk for neuropsychiatric symptoms in Alzheimer's disease: the Cache County Study. *Int Psychogeriatr.* (2008) 20:538–53. doi: 10.1017/S1041610208006704

102. Hassing LB, Dahl AK, Thorvaldsson V, Berg S, Gatz M, Pedersen NL, et al. Overweight in midlife and risk of dementia: a 40-year follow-up study. *Int J Obes.* (2009) 33:893–8. doi: 10.1038/ijo.2009.104

103. Tini G, Scagliola R, Monacelli F, La Malfa G, Porto I, Brunelli C, Rosa GM. Alzheimer's disease and cardiovascular disease: a particular association. *Cardiol Res Pract.* (2020) 2020:2617970. doi: 10.1155/2020/2617970

104. Sparks DL, Scheff SW, Liu H, Landers TM, Coyne CM, Hunsaker III JC. Increased incidence of neurofibrillary tangles (NFT) in non-demented individuals with hypertension. *J Neurol Sci.* (1995) 131:162–9. doi: 10.1016/0022-510X(95)00105-B

105. Murphy SJ, Werring DJ. Stroke: causes and clinical features. *Medicine (Baltimore).* (2020) 48:561–6. doi: 10.1016/j.mpmed.2020.06.002

106. Hachinski V, Einhäupl K, Ganten D, Alladi S, Brayne C, Stephan BC, et al. Preventing dementia by preventing stroke: the Berlin Manifesto. *Alzheimers Dement.* (2019) 15:961–84. doi: 10.1016/j.jalz.2019.06.001

107. Loera-Valencia R, Cedazo-Minguez A, Kenigsberg P, Page G, Duarte A, Giusti P, et al. Current and emerging avenues for Alzheimer's disease drug targets. *J Intern Med.* (2019) 286:398–437. doi: 10.1111/joim.12959

108. Kuljiš RO, Šalković-Petrišić M. Dementia, diabetes, Alzheimer's disease, and insulin resistance in the brain: progress, dilemmas, new opportunities, and a hypothesis to tackle intersecting epidemics. *J Alzheimers Dis.* (2011) 25:29–41. doi: 10.3233/JAD-2011-101392

109. Ponce-López T, Sorsby-Vargas AM, Bocanegra-López AP, Luna-Muñoz J, Ontiveros-Torres MA, Villanueva-Fierro I, et al. Diabetes mellitus and amyloid beta protein pathology in dementia. In: *Amyloid Diseases*. London: IntechOpen (2019) doi: 10.5772/intechopen.84473

110. Nelson L, Gard P, Tabet N. Hypertension and inflammation in Alzheimer's disease: close partners in disease development and progression! *J Alzheimers Dis.* (2014) 41:331–43. doi: 10.3233/JAD-140024

111. Skoog I, Gustafson D. Update on hypertension and Alzheimer's disease. *Neurol Res.* (2006) 28:605–11. doi: 10.1179/016164106X130506

112. Benetos A, Thomas F, Safar ME, Bean KE, Guize L. Should diastolic and systolic blood pressure be considered for cardiovascular risk evaluation: a study in middle-aged men and women. *J Am Coll Cardiol.* (2001) 37:163–8. doi: 10.1016/S0735-1097(00)01092-5

113. Katayama T, Hasebe N. Angiotensin-receptor blockers, hypertension and Alzheimer disease-the entangled relationship. *Circ J.* (2013) 77:315–6. doi: 10.1253/circj.CJ-12-1550

114. Iadecola C. Hypertension and dementia. *Hypertension.* (2014) 64:3–5. doi: 10.1161/HYPERTENSIONAHA.114.03040

115. World Bank. *World Bank Country and Lending Groups 2020* (2020).

116. Zhou B, Lu Y, Hajifathalian K, Bentham J, Di Cesare M, Danaei G, et al. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet.* (2016) 387:1513–30. doi: 10.1016/S0140-6736(16)00618-8

117. Turana Y, Tengkawan J, Chia YC, Hoshide S, Shin J, Chen C-H, et al. Hypertension and Dementia: a comprehensive review from the HOPE Asia Network. *J Clin Hypertens.* (2019) 21:1091–8. doi: 10.1111/jch.13558

118. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global disparities of hypertension prevalence and control. *Circulation.* (2016) 134:441–50. doi: 10.1161/CIRCULATIONAHA.115.018912

119. Piff PK, Stancato DM, Côté S, Mendoza-Denton R, Keltner D. Higher social class predicts increased unethical behavior. *Proc Natl Acad Sci USA.* (2012) 109:4086–91. doi: 10.1073/pnas.1118373109

UNIVERSIDAD
DE BURGOS

Síntesis empírica de meta-análisis, técnicas de optimización multi-objetivo y minería de datos aplicadas al diagnóstico de la Enfermedad de Alzheimer