CAPÍTULO 13

CARDIOVASCULAR RISK FACTORS IN ALZHEIMER'S DISEASE-A META-ANALYSIS

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INTRODUCTION

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 (Martin, Anders, y Maëlenn 2015). 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 (Leyhe et al. 2017). Describe some of the main risk vascular factors (cholesterol, blood pressure, and stroke) found in the scientific literature, could be 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 (Zurique Sánchez et al. 2019). Therefore, 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 (Jorgensen et al. 2008).

Among more important vascular risk factors are cholesterol, blood pressure, and stroke (Mayeux y Stern 2012; Silva et al. 2019). 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 cholesterol, blood pressure, and stroke – 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 (Regalado Doña et al. 2009). The coexistence of anatomopathological lesions typical of AD and vascular lesions has been demonstrated by autopsy (Kalaria 2000). 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 (Luchsinger et al. 2004). On the other hand, depression may confer an increased risk of developing AD in the future. Therefore, the aimed of this review of meta-analyses

was determine and analyze some of the risk factors (cholesterol, blood pressure, and stroke) associated with AD.

METHOD

This meta-meta-analysis was performed in accordance with the Preferred Reporting for Systematic Reviews and Meta-analysis (PRISMA) Statement (Urrutia y Bonfill 2010). For data collection, we searched meta-analyses that measured cholesterol, blood pressure, and stroke 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 in the last three years (2020-2023). Combinations of the following search terms were used: "cholesterol" AND "blood pressure" AND "stroke" AND "Alzheimer's disease" AND "meta-analysis". The data search was done in English.

By consensus of the authors, studies were included if they met the following criteria: Meta-analysis that investigates the effect of cholesterol, blood pressure, and stroke (at baseline) as an antecedent to AD (follow-up); patients with a diagnosis of AD according to diagnosis criteria and original, peer-reviewed meta-analyses that were published in English. The following were excluded: not published as meta-analyses in peer-reviewed journals; Studies investigating the association of cholesterol, blood pressure, and stroke and risk of AD using a sample of patients with AD and other dementia (non-independent or overlapping data for AD).

Titles and abstracts of potential meta-analyses about cholesterol, blood pressure and stroke and incident AD were independently analyzed by three researchers (OS, SU, AP). After exclusion of irrelevant articles, the remaining meta-analyses were critically inspected to check data accuracy. The lead author and either the second 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 cholesterol, blood pressure and stroke and AD.

Crude odds ratios (ORs) (and 95% confidence intervals (CIs)) were used to calculate the risk of developing AD associated with previous cholesterol, blood pressure or stroke. Summary statistics were calculated using Comprehensive Meta-Analysis software (CMA; Version 3) (Biostat Inc., Englewood, NJ, USA) (Borenstein et al. 2007, 2011). Initially, we performed an analysis summarizing all data available, including all studies with validated cut-offs or clinical diagnoses in a single pooled estimate (Borenstein et al. 2011). 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(Reis y Judd 2000). Presence of publication bias was assessed through visual inspection of funnel plots and with Egger's test (Reis y Judd 2000).

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). Therefore, we calculated the effect sizes of the association between cholesterol, blood pressure and stroke and risk of AD separately.

RESULTS

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 (Sáiz-Vazquez et al. 2020). 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.

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. However, the results showed no difference in serum HDL levels between healthy and AD subjects. Triglyceride (TG) levels also did not show a positive association with the development of AD. As for TC (total cholesterol), the results found no significant effect of TC levels on AD.

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.

Table 1. 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
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

Blood presure and ad

In the second meta-analysis, the association between elevated blood pressure (BP) and the risk of developing AD was studied(Sáiz-Vázquez et al. 2021). 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. In relation to combined arterial hypertension (CAP) (i.e. high SBP and DBP), elevated BP was not associated with an increased risk of developing AD.

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. 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). 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.

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. In addition, an association was also found between HS (Hemorrhagic Stroke) and the risk of developing AD. Finally, a significant association was found between MI (microinfarcts) and AD.

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). Age was not a factor when studying the association between all types of stroke and AD, and between MI and AD. 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.

This meta-analysis 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.

All the risk factors and ad

Pooling all the effects extracted from the meta-analyses performed with the different risk factors, the largest effect sizes are for: 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.

DISCUSSION

Cholesterol and ad

The overall results revealed that cholesterol level is a risk factor for AD (Feringa y van der Kant 2021). 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 (Feringa y van der Kant 2021). 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 (Hall et al. 2014).

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 (Liu et al. 2020; Tan et al. 2003; Wu et al. 2019; Xu et al. 2015); but, in other studies, lower HDL levels have been associated with a higher risk of developing AD (Carleton et al. 1991; Reitz et al. 2004). 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 (Button et al. 2019).

Triglyceride (TG) levels also did not show a positive association with the development of AD. Triglycerides are a type of lipoprotein that accumulate in the arteries and can produce adverse side effects in the human body (Laufs et al. 2020). 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 (Jick et al. 2000; Wolozin et al. 2000).

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 (Button et al. 2019; Tan et al. 2003; Zhou et al. 2020). 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.

Blood presure and ad

The results showed that participants with elevated SBP were at an increased risk of developing 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 (Kuljiš y Šalković-Petrišić 2011; Nelson, Gard, y Tabet 2014; Ponce-López et al. 2019).

In relation to 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. (Guan et al. 2011).

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. Some studies have linked hypertension to brain atrophy, white matter lesions, and neurofibrillary tangles (Duron y Hanon 2008). 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

(Duron y Hanon 2008; Knecht et al. 2008). Thus, there is evidence that pathologies of vascular origin play an important role in the etiology of AD.

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 (Chen et al. 2010).

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 (Tolppanen et al. 2013; Waziry et al. 2020). Finally, a significant association was found between MI (microinfarcts) and AD. Previous studies also demonstrated an association between MI and AD. (Ferro et al. 2019; Saposnik et al. 2009). In fact, MI may alter important cognitive networks and thus explain part of the neurological dysfunction suffered by the brain in AD (Smith et al. 2012).

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. (Kawas et al. 2000) 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. (Michalski et al. 2018), 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. 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 (Paterson et al. 2018).

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.

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 (Imtiaz et al. 2014).

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.

CONCLUSIONS

These results strengthen the evidence that the risk factors related to cardiovascular diseases increase risk for AD. Moreover, moderator analysis supports the robustness of our results. Therefore, future studies should use other uncontrolled factors, such as diabetes, to explain the relationship between these variables.

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