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Physical Condition and Risk of Hospitalization and Polypharmacy in Older Adults

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REPLY TO REVIEWER
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Comments to the Author. The authors have presented data on a topic of relevance on the effect of being in good physical condition and the risk of hospitalization and polypharmacy in older persons. However, some areas of the manuscript could be improved upon the addition of the below mentioned suggestions.

Reply: All the authors are grateful for the helpful and constructive criticisms of this reviewer. We feel the comments made have certainly helped us improve the description of our work. We have applied all your recommendations with effort. We hope they meet the quality standards that this reviewer aspires to.

Point 1. Page 4. "However, few studies have examined the relationship between physical function and polypharmacy.8,9"

Comment: Does this statement still hold true since there are more recent literature on polypharmacy and frailty [https://www.hindawi.com/journals/jar/2020/6759521/]?

Reply: The frailty phenotype defines frailty as a distinct clinical syndrome meeting three or more of five phenotypic criteria: weakness, slowness, low level of physical activity, self-reported exhaustion, and unintentional weight loss. The frailty index defines frailty as cumulative deficits identified in a comprehensive geriatric assessment. In most studies found in the literature, handgrip strength is considered the only biomarker for frailty [1]. In fact, it is associated with overall health status, physical function decline, malnutrition and is a relevant predictor of all-cause mortality [2]. Several studies show that low HGS is associated with various indicators of frailty [3-4] since it is a sign of overall muscle weakness and sarcopenia [5-6], an age-related decline in muscle mass that leads to the loss of muscle fibers [7]. However, we have included other markers of physical function in addition to HGS. This is why we considered only few studies have examined the relationship between physical function and polypharmacy.

1. Bohannon, R.W. Grip Strength: An Indispensable Biomarker For Older Adults. *Clin. Interv. Aging* **2019**, *14*, 1681–1691. [CrossRef] [PubMed]
2. Soysal, P.; Hurst, C.; Demurtas, J.; Firth, J.; Howden, R.; Yang, L.; Tully, M.A.; Koyanagi, A.; Ilie, P.C.; Lopez-Sanchez, G.F.; et al. Handgrip strength and health outcomes: Umbrella review of systematic reviews with meta-analyses of observational studies. *J. Sport Health Sci.* **2020**, *10*, 290–295. [CrossRef] [PubMed]

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3. Coelho, T.; Santos, R.; Paúl, C.; Gobbens, R.J.; Fernandes, L. Portuguese version of the Tilburg Frailty Indicator: Transcultural adaptation and psychometric validation. *Geriatr. Gerontol. Int.* **2015**, *15*, 951–960. [CrossRef] [PubMed]

4. Reeve, T.E.t.; Ur, R.; Craven, T.E.; Kaan, J.H.; Goldman, M.P.; Edwards, M.S.; Hurie, J.B.; Velazquez-Ramirez, G.; Corriere, M.A. Grip strength measurement for frailty assessment in patients with vascular disease and associations with comorbidity, cardiac risk, and sarcopenia. *J. Vasc. Surg.* **2018**, *67*, 1512–1520. [CrossRef] [PubMed]

5. Sousa-Santos, A.R.; Amaral, T.F. Differences in handgrip strength protocols to identify sarcopenia and frailty—A systematic review. *BMC Geriatr.* **2017**, *17*, 238. [CrossRef] [PubMed]

6. Dodds, R.M.; Syddall, H.E.; Cooper, R.; Kuh, D.; Cooper, C.; Sayer, A.A. Global variation in grip strength: A systematic review and meta-analysis of normative data. *Age Ageing* **2016**, *45*, 209–216. [CrossRef] [PubMed]

7. Siparsky, P.N.; Kirkendall, D.T.; Garrett, W.E., Jr. Muscle changes in aging: Understanding sarcopenia. *Sports Health* **2014**, *6*, 36–40. [CrossRef]

Point 2. "in older people, the present study was designed to explore the possible modulating role of physical fitness, its associated polymorphisms, as well as nutrition status, quality of life and"

Comment: What is meant by "associated polymorphism"? I think the above statement could be written more clearly.

Reply: Thank you for the comment. We have added the information.

Point 3. Page 5. How were participants recruited and what is the baseline statistics. Were participants from diverse ethnicity and race? Otherwise, it would be nice to examine how these differences affected the study and if it was skewed towards a particular ethic group or race.

Reply: Thank you for the comment. We have added the information. All recruited participants were Caucasian descendent from three or more generations.

Point 4. It would be nice to expatiate on the rationale of some of the test being carried out as not all readers would be familiar with them.

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Reply: Thank you for the comment. We have added the information.

Point 5. How long did the study last and did the study have a control group from the start?

Reply: We were recruiting the subjects during 6 months. The objective of the study was not a case control design that is why we had not control group.

Point 6. Page 9. From the authors understanding is there a reason why the OR for the Chair stand test result lost its significance after adjusting for sex and age?

Reply: Chair stand test result lost its significance after adjusting for sex and age. The reduction in physical function might also be an indication that inactivity leads to this cut-off point, in accordance with the "use it or lose it" theories, rather than biological phenomena alone. Furthermore, the less active lifestyle and a withdrawal from society might be a result of and related to a complex and difficult environmental context that hinders everyday activities, like walking to the shop or other outdoor activities [8].

8. Spirduso W, Francis KL, MacRae PG. Physical dimensions of aging, 2nd edition. Champaign, IL: Human Kinetics; 2005

Point 7. Page 10. Reference needed here - "Having a higher score in the Chair stand test was found to reduce the risk of hospitalization and a need for more medication. This test is considered a key indicator of lower body strength."

Reply: Thank you for the comment. We have added the information.

Point 8. The statement below could be made clearer as its my understanding that "physical fitness polymorphism" is not associated with hospitalization. A distinction between 'physical condition' and ''physical fitness polymorphism" has to made to make the discussion clearer.

Reply: Thank you for the comment. We have added the information.

Point 9. "Finally, neither was any link observed between dietary habits, nutritional status, and physical fitness related polymorphisms, and the dependent variables polypharmacy or risk of hospitalization."

REPLY TO REVIEWER
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Reply: It is traditionally assumed that successful aging results from the combination of genetic and environmental factors. In particular, the existence of SNPs linked with physical performance suggests the intriguing possibility of identifying individuals at risk of functional impairment, hospitalization or polypharmacy, at an early stage, therefore allowing for interventions to be implemented in a timely manner. It should be considered that complex age-related phenotypes, such as those investigated in the present work, are influenced by a wealth of biological pathways involving multiple genes. The individual effects of SNPs may therefore be expected to be very small and difficult to identify. To further complicate the matter, the impact of genetic factors is likely modulated by social and environmental factors or may be mediated by some other endophenotypes, including inflammation. As such, the association of genetic variants with certain phenotypes may be environment-specific and therefore hardly replicable across cohorts [9].

9. Heckerman, D., Traynor, B.J., Picca, A. et al. Genetic variants associated with physical performance and anthropometry in old age: a genome-wide association study in the ilSIRENTE cohort. Sci Rep 7, 15879 (2017). https://doi.org/10.1038/s41598-017-13475-0

Point 10. Page 10. The user to expatiate on terms used such as “instrumental ADL” for more understanding to a wider audience. Also, it may be helpful to offer suggestions on why associations were found with physical conditions but not with ADL and why better physical conditions may not translate to links with ADL.

Reply: Thank you for the comment. We have added the information.

Point 11. Were there any limitations of the study?

Reply: Thank you for the comment. We have added the information.

Point 12. Overall, the authors should provide more explanation on the novelty of this study since previous studies have alluded to the benefits of physical condition on the risk of hospitalization and polypharmacy.

Reply: We hypothesized that some genetic variants could also be an important factor influencing the quality of life and the functional autonomy of older people. Only a few studies have addressed the association between physical performance measures and polypharmacy in the elderly. Moreover, we have included genetic factors in our analysis.

REPLY TO REVIEWER
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It is traditionally assumed that successful aging results from the combination of genetic and environmental factors. In particular, the existence of SNPs linked with physical performance suggests the intriguing possibility of identifying individuals at risk of functional impairment, hospitalization or polypharmacy, at an early stage, therefore allowing for interventions to be implemented in a timely manner. It should be considered that complex age-related phenotypes, such as those investigated in the present work, are influenced by a wealth of biological pathways involving multiple genes. The individual effects of SNPs may therefore be expected to be very small and difficult to identify. To further complicate the matter, the impact of genetic factors is likely modulated by social and environmental factors or may be mediated by some other endophenotypes, including inflammation. As such, the association of genetic variants with certain phenotypes may be environment-specific and therefore hardly replicable across cohorts.

Physical Condition and Risk of Hospitalization and Polypharmacy in Older Adults

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Key words: Aging, activities of daily living, quality of life, exercise, health status, prevention

ABSTRACT

Hospitalization in older population leads to a decline in physical function, physical condition and independency. However, a scarce number of studies has addressed the effect of being in good physical condition on the risk of hospitalization and polypharmacy in older people. Therefore, this study aims to examine the relationship between physical condition and other health factors, and the incidence of hospitalization and polypharmacy in Spanish older persons. For this cross-sectional study 102 community-dwelling persons aged 80 years or older who were being treated at three primary care centers. The data collected were number of hospitalizations and medications, dietary habits, nutrition status, quality of life, independence in activities of daily life, physical performance and associated genotype data. Scoring higher in the tests Chair stand and 8-Foot Up-and-go was found associated with reduced risks of hospitalization [OR = .45 (95% CI = .2, .99); OR .32 (95% CI = .12, .86)] and polypharmacy [OR = .36 (95% CI = .16, .8); OR= .28 (95% CI = .1, .78)]. The number of medications was also lower in individuals with a greater aerobic capacity and activities of daily life independence [OR = .28 (95% CI = .1, .78); OR = .37 (95% CI = .16, .82)]. No associations were found with the remaining physical performance tests or other factors assessed. Our findings point to benefits of greater strength, balance and aerobic capacity in terms of reducing the risk of hospitalization and polypharmacy.

INTRODUCTION

Ageing is accompanied by a gradual decline in physiological reserves that leads to an increased risk of adverse health outcomes. The term physical condition, also referred to as physical functioning, is used to describe an individual's capacity to undertake the physical tasks of everyday living.[1] Today there is evidence to suggest that certain measures of physical capability may be predictive of subsequent health problems in older adults.[2,3] In a systematic review, Cooper et al.[1] identified 24 studies examining correlation between specified measures of physical capacity and the risk of specific health outcomes. These authors concluded that lower levels of physical activity were associated with a greater risk of having health problems. In addition, a weaker grip strength and slower walking speed were found associated with an increased risk of future fractures and cognitive decline. Physical condition in older people has been also directly linked to health-related quality of life.[4]

Hospitalization in older population leads to a decline in physical function, physical condition and independency.[5] Thus, several studies have found that older patients hospitalized because of acute illness will show reduced independence in activities of daily living (ADL) and health related quality of life (HRQL) after hospital discharge.[6,7] However, few studies have examined the relationship between physical function and polypharmacy.[8,9] Functional capacity is an example of a complex trait (those under the influence of many genes, environmental factors, and gene–environment interactions).[10–12] It is important to understand how ageing and its interactions with lifestyle and genetic factors affect physical fitness in diverse set of populations.

Understanding the genetic influences on functional capacities should be done in a diverse set of populations. Studies assessing the contribution of genetic polymorphisms to age-related diminished physical fitness and subsequent loss of independence are of broad interest owing to our ever-increasing longevity and accompanying health problems.

Given the scarcity of studies that have addressed the effect of being in good physical condition on the risk of hospitalization and polypharmacy in older people, the present study was designed to explore the possible modulating role of physical fitness, genetic variants related to functional capacities, as well as nutrition status, quality of life and ADL independence on the incidence of hospital admissions and polypharmacy in community-dwelling octogenarians.

MATERIALS AND METHODS

Participants

The study protocol adhered to the principles of the Declaration of Helsinki 2008[13] and received local review board approval (Ref. CEIC 1446). The use of retrospective data from the primary care patient database was approved by each institution's ethics committee. All participants provided their written informed consent following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[14]

For this cross-sectional study, we recruited 102 (58 women) institutionalized octogenarians (85.7±3.9 years). All recruited participants were Caucasian descendants from three or more generations. Inclusion criteria were: women and men aged over 80 years of age who were clinical stable (i.e. no hospitalization within the last 6 months). Subjects were

excluded if they had dementia or restricted mobility. To assess cognitive status, the mini mental status examine was used.[15] Mobility was assessed through the ability to walk without any aid for more than 2 minutes.[16]

Measures

In each participant, number of hospitalizations for any cause in the last year and number of drugs taken were collected from their medical records. Then, each subject was examined by a research nurse who collected the quality of life measures Barthel Index (BI), EuroQol 5-Dimensions (EQ-5D), and EuroQol Visual Analogue scale (EQ-VAS). BI is used to assess independence in ADL.[17] The EQ-5D questionnaire evaluates HRQL including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The results are combined in a unique parameter corresponding to the participant's health state and then a final EQ-5D index is calculated, it is validated in Spanish population and can be applied for a wide range of health conditions and treatments.[18] EQ-VAS is a quantitative measure of HRQL judged by the individual.[18] The advantages of this questionnaire are that it is short, easy to complete, and simple to understand.[19]

Physical function was assessed through the Senior Fitness test[20] including six tests of strength, muscle endurance, aerobic endurance, flexibility, agility and balance. A more detailed description of the items in the Senior Fitness Test is as follows: upper and lower body strength were assessed using the biceps curl and 30-second Chair stand test respectively. For aerobic endurance, we used the Two-minute step test. The Chair sit-and-reach was used for lower body flexibility and the Back scratch for upper body flexibility. Agility and dynamic balance were measured through the 8-Foot Up-and-go test. The Senior

Fitness test can be very useful in the work of primary prevention as motivator for physical activity in risk groups of elderly people and is tested for reliability, with an intra-class correlation coefficient (ICC) ranging from 0.8 to 0.98 on the different items.[21,22] Muscle strength was measured as hand grip strength (HGS) after adjustment for hand size, HGS was measured in the dominant hand (the average score of three measures was used in the analyses) by a maximal isometric test using a hand dynamometer.[23]

Adherence to the Mediterranean diet was assessed through a 14-item questionnaire validated by PREDIMED (PREvención con DIeta MEDiterránea).[24] Nutrition status was assessed through the Mini Nutritional Assessment (MNA).[25]

For genetic testing, genomic DNA was extracted from buccal cells according to standard phenol/chloroform procedures followed by alcohol precipitation. Allelic discrimination analysis was performed with pre-designed Life Technologies TaqMan® SNP Genotyping Assays on demand for the polymorphisms: ***ACTN3*** rs1815739 (ID: C_590093_1_), ***PPARGC1A*** rs8192678 (ID: C_1643192_20), ***BDNF*** rs6265 (ID: C_11592758_10), and ***CKM*** rs8111989 (ID: C_3145002_10). For ***APOE*** genotyping, we considering two SNPs: Cys112Arg (rs429358) (ID: C_3084793_20) and Arg158Cys (rs7412) (ID: C_904973_10). Individuals designated ε2 were carriers of alleles 112Cys and 158Cys, those designated ε3 were carriers of alleles 112Cys and 158Arg, and those designated ε4 were carriers of alleles 112Arg and 158Arg. PCR amplifications were performed using a StepOne™ Real-Time PCR System (Life Technologies, Foster City, CA) with a denaturation stage at 95°C for 10 min, 50 cycles of denaturation at 92°C for 15 s, annealing/extension at 60°C for 1 min, and a final extension stage of 30 s at 60°C. Allelic

discrimination analysis for the ***ACE* I/D** polymorphism was performed by PCR followed by electrophoresis on a 1.5% agarose gel containing ethidium bromide. The primers used were: 5'- CTGGAGAGCCACTCCCATCCTTTCT and 5'-GACGTGGCCATCACATTCGTCAGAT.[26] The fragments amplified were a 190 bp product for allele D (allele without insertion) and a 490 bp product for allele I (allele with insertion). To avoid misclassification of ID heterozygotes as DD homozygotes, a second PCR reaction was performed in all samples initially classified as DD with the insertion-specific primer pair: 5'-TGGGACCACAGCGCCCGCCACTAC and 5'-TCGCCAGCCCTCCCATGCCCATAA.[27] Only allele I produced a 335 bp fragment identified on a 1.5% agarose gel stained with ethidium bromide.

Statistics

Some of variables were recoded or dichotomized due to the data distribution and limited sample size. Dependent variables were grouped using the median as the cut-off. In the case of hospitalizations, the median was 0.5, so participants were classified as those not hospitalized in the last year and those hospitalized 1 or more times during the last year. For the number of drugs prescribed to each participant, the median was 5, so individuals were grouped into those taking fewer than 5 drugs a day and those taking 5 drugs or more. The results of the physical and functional exams were recoded into 2 groups: poor physical condition (cannot perform the exam, very poor or poor result) or good physical condition (medium, good or very good result).

To explore relationships among variables, binomial logistic regression models were constructed using hospitalizations and drugs taken as the dependent variables. First,

uncorrected regression models were built reporting the odds ratio (OR) and p-value. Then, models adjusted for sex and age were constructed. Significance was set at $p < 0.05$. All statistical tests were performed using the software package SPSS v.21.0.

RESULTS

Participant characteristics

Most subjects lived in urban areas (62%) in nursing homes (55%). Most were agricultural workers (50%) and most of them had not gone to school (50%). At the time of this study, 61% reported they carried out leisure activities with their friends outside the home, while the rest spent their day at the home. They were mainly non-smokers (87%) and non-drinkers (78%).

Physical fitness, quality of life and hospitalization risk

Table 1 shows the likelihood of a person being hospitalized in relation to the results of the physical condition tests. Obtaining a good result in the Chair stand test reduced by .45 (95% CI = .2, .99) times the likelihood of being hospitalized, while obtaining a poor result was found to increase the chances of hospitalization by 2.22 times. In addition, a good result in the 8-Foot Up-and-go test decreased this likelihood by .32 (95% CI = .12, .86) times, and a poor result increased the hospitalization risk by 3.125 times. After adjusting for sex and age, the OR for the Chair stand test result lost its significance.

The remaining components of the Senior fitness test, i.e. hand grip and quality of life measures (BI and EQ-5D) were not significantly associated with hospitalization risk.

Physical fitness, quality of life and polypharmacy

Some of the physical fitness test results were also correlated with a reduced likelihood of polypharmacy (**Table 2**). This meant that a good result in the Chair stand test reduced the possibility of having a high medication burden by .36 (95% CI = .16, .8) times, and a poor result increased this possibility by 2.77 times. Also, a high score in the 8-Foot Up-and-go test reduced the likelihood of polypharmacy burden by 0.28 (95% CI = .1, .78) times and a low score increased this risk 3.514-fold. Having a high aerobic capacity lowered by .24 (95% CI = .1, .62) the probability of polypharmacy and a low capacity increased this probability by 4.166 times. In addition, polypharmacy was related to a lower quality of life according to the EQ-5D questionnaire (OR = .37; 95% CI = .16, .82), such that the likelihood of having a better quality of life was reduced by 2.702 times.

The results of the remaining physical fitness tests and BI could not be related to polypharmacy.

No impacts of survival, physical fitness-related polymorphisms, and nutritional habits on hospitalization and medication burden

No effects were observed between the different physical fitness-related polymorphisms examined and the probability of hospitalization or polypharmacy (**Supplementary Table 1)**.

Having a normal nutritional status or risk of malnutrition as assessed with MNA was not associated with hospitalization risk or with the probability of a high medication burden. Neither was showing better adherence to the Mediterranean diet linked to a greater risk of hospitalization or polypharmacy (**Supplementary Table 2)**.

DISCUSSION

Our study reveals an existing relationship between certain measures of physical performance and the prevalence of hospitalization and a higher drug burden in octogenarians. Having a higher score in the Chair stand test was found to reduce the risk of hospitalization and a need for more medication. This test is considered a key indicator of lower body strength.[28]

Maintaining lower body strength during ageing is important to prevent or delay dependency, physical fragility and disability.[29] In addition, having a good score in the 8-Foot Up-and-go test was also associated here with a lower prevalence of hospitalization and polypharmacy. Further, aerobic endurance, measured through the Two-minute step test, was inversely associated with drug use, but not with hospitalization prevalence. Further, a worse HRQL, assessed using the EQ-5D questionnaire, was associated with polypharmacy, but not with BI-assessed ADL independence. No associations with hospitalization risk were detected for quality of life or independence in ADL. Finally, neither was any link observed between dietary habits, nutritional status, and the dependent variables polypharmacy or risk of hospitalization. In addition, we didn´t observe any relationship between genetic polymorphisms related to physical fitness and polypharmacy or risk of hospitalization.

So far, there is evidence to suggest that polypharmacy may be related to an older age, socio-economic factors, institutionalization and a poor health status.[30] However, the relationship between physical condition and polypharmacy has been hardly explored.[8,9,30] Here, we noted that older adults showing worse lower body strength, agility and aerobic capacity have a greater risk of polypharmacy. In agreement with this finding, Sganga et al.[8]

found a significant association between muscular strength and polypharmacy in hospitalized patients who were under treatment with more than 10 different drugs.

The ability to perform ADL is affected by the functional decline that older individuals experience. However, in our study no association was observed between ADL and hospitalization risk or polypharmacy. Other authors have nevertheless reported this variable –ADL function– is a risk factor for hospitalization in older people. Thus, the worse stage of ADL and instrumental ADL have been linked to a risk of first hospitalization,[31] and also with hospital admittance days and visits to the family doctor in the past months.[32] Moreover, instrumental ADL (activities that allow an individual to live independently in a community as cooking, cleaning, transportation or laundry) has been linked to both polypharmacy and excessive polypharmacy.[33] Dwyer et al.[34] found that older persons needing assistance in five ADLs had a lower risk of polypharmacy than those receiving assistance in four or fewer ADLs. Another investigation was unable to find differences in the number of impaired ADLs between individuals requiring polypharmacy (>5 drugs) or not.[8]

Despite the fact that we were unable to detect any association between nutritional status and polypharmacy or hospitalization risk, currently there is evidence to show that these variables are related. Several factors can cause malnutrition such as illness, hospitalization or drug intake.[35] Remarkably, ageing is a cause of malnutrition.[36] Moreover, the prevalence of malnutrition in hospitalized older people is increasing all over the world[36] and this will have several consequences such as increasing morbidity and mortality from disease, impairing recovery, increasing treatment costs and prolonging treatment duration.[35] In a

systematic review of six longitudinal studies conducted in 2016, polypharmacy emerged as a risk factor for malnutrition in older women but not in men.[37]

This study has several limitations. For example, muscle strength is a complex trait, which is likely influenced by numerous genes and genetic variants, as well as other environmental factors that may be interacting with these genes in several pathways. In addition, the sample group was small, which may have reduced the statistical power. On the other hand, despite the small sample size of the current study, our population was homogeneous and well defined in terms of phenotype assessment.

Genetic variants associated with aging may help identify factors amenable to interventions aimed at improving the quality of life of older adults. In particular, the existence of SNPs linked with physical performance suggests the intriguing possibility of identifying individuals at risk of functional impairment at an early stage, therefore allowing for interventions to be implemented in a timely manner.

We hypothesized that some genetic variants could also be an important factor influencing the quality of life and the functional autonomy of older people. The genetic polymorphisms selected for our study affect genes described to play an important role in traits related to physical performance (ACTN3, PGC1A, CKM and ACE) and in conditions associated with ageing such as dementia and a worse HRQL (APOE and BDNF).[38] However, our results did not serve to identify any significant relationships between these genetic variants and the likelihood of requiring hospitalization or polypharmacy. This finding could perhaps be explained by the multifactorial nature of these variables, which could involve a greater number of genes, or genes with more impacts than the few examined here.

CONCLUSIONS

In conclusions, our findings indicate that the octogenarians examined here performing better at the Chair stand and 8-Foot Up-and-go test showed a lower risk of hospitalization and polypharmacy. In addition, the risk of needing more drugs was also reduced by an improved aerobic capacity and independence in activities of daily living. No associations were, nevertheless, found with the remaining physical performance tests, dietary habits, nutritional status, quality of life and physical fitness-related genetic polymorphisms. In prior work, we reported that physical training may benefit older adults by improving their physical condition, HRQL and preventing a wide range of chronic diseases.[39] Thus, we could speculate that improving the physical fitness of our older people could offer numerous benefits for everybody. It is traditionally assumed that successful aging results from the combination of genetic and environmental factors. In particular, the existence of SNPs linked with physical performance suggests the intriguing possibility of identifying individuals at risk of functional impairment, hospitalization or polypharmacy, at an early stage, therefore allowing for interventions to be implemented in a timely manner. It should be considered that complex age-related phenotypes, such as those investigated in the present work, are influenced by a wealth of biological pathways involving multiple genes. The individual effects of SNPs may therefore be expected to be very small and difficult to identify. To further complicate the matter, the impact of genetic factors is likely modulated by social and environmental factors or may be mediated by some other endophenotypes, including

inflammation. As such, the association of genetic variants with certain phenotypes may be environment-specific and therefore hardly replicable across cohorts.[40]

Disclosure statement: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Author contribution: A.F.A., C.S., H.P.G. and Z.V. conceived and designed the investigation; A.F.A., L.G.D., M.M.F., T.Y., and T.M. collected the data; I.D.V., C.S., H.P.G. and Z.V. performed the analysis and interpreted the data; A.F.A., L.G.D., M.M.F., H.P.G. and Z.V. drafted the paper; All authors have approved the final version and agreed to publish this version of the manuscript.

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Table 1. Logistic regression analysis of the association between risk of hospitalization and the results of physical fitness and quality of life tests

		Model 1 (crude)		Model 2 (adjusted for sex and age)	
	n (%)	OR (CI95%)	p	OR (CI95%)	p
Physical performance					
Chair stand					
Good	46 (45)	**.45 (.2-.99)**	**.048**	.45 (.2-1)	.050
Poor	56 (55)	ref.		ref.	
8-Foot Up-and-go					
Good	23 (24)	**.32 (.12-.86)**	**.024**	**.32 (.12-.89)**	**.029**
Poor	74 (76)	ref.		ref.	
Aerobic capacity					
Good	31 (34)	.61 (.25-1,45)	.262	.64 (.26-1,55)	.319
Poor	59 (66)	ref.		ref.	
Biceps curl					
Good	73 (72)	.62 (.26-1,47)	.274	.66 (.27-1,6)	.354
Poor	29 (28)	ref.		ref.	
Sit-and-reach					
Good	61 (60)	.69 (.31-1,55)	.372	.69 (.31-1,56)	.373
Poor	40 (40)	ref.		ref.	
Back scratch					
Good	8 (8)	.59 (.13-2,6)	.483	.52 (.11-2,45)	.408
Poor	93 (92)	ref.		ref.	
Hand grip					
Good	47 (51)	.52 (.23-1,19)	.121	.44 (.14-1,35)	.150
Poor	46 (49)	ref.		ref.	
Quality of life					
Barthel					
Independent or low dependence	77 (75)	1,11 (.45-2,74)	.818	1,17 (.52-2,62)	.702
Dependence	25	ref.		ref.	

	(25)				
EuroQol					
Good	54 (53)	.73 (.33-1,59)	.428	.8 (.36-1,78)	.582
Poor	48 (47)	ref.		ref.	

OR odds ratio, CI confidence interval, p probability of significance. In bold: significant OR, CI or p-values

Table 2. Logistic regression analysis of the association between polypharmacy and the results of physical fitness and quality of life tests

		Model 1 (Crude)		**Model 2 (Adjusted for sex and age)**	
	n (%)	OR (CI95%)	p	OR (CI95%)	p
Physical performance					
Chair stand					
Good	46 (45)	**.36 (.16-.8)**	**.013**	**.36 (.16-.8)**	**.013**
Poor	56 (55)	ref.		ref.	
8-Foot Up-and-go					
Good	23 (24)	**.28 (.1-.78)**	**.015**	**.28 (.1-.78)**	**.015**
Poor	74 (76)	ref.		ref.	
Aerobic capacity					
Good	31 (34)	**.24 (.1-.62)**	**.003**	**.24 (.09-.62)**	**.003**
Poor	59 (66)	ref.		ref.	
Arm Curl					
Good	73 (72)	.76 (.32-1,81)	.529	.77 (.32-1,86)	.554
Poor	29 (28)	ref.		ref.	
Sit and Reach					
Good	61 (60)	.68 (.3-1,53)	.350	.68 (.3-1,53)	.352
Poor	40 (40)	ref.		ref.	
Back scratch					
Good	8 (8)	.33 (.06-1,74)	.192	.31 (.06-1,69)	.175
Poor	93 (92)	ref.		ref.	
Hand grip					
Good	47 (51)	.5 (.22-1,14)	.099	.36 (.11-1,16)	.086
Poor	46 (49)	ref.		ref.	
Quality of life					
Barthel					
Independent or low dependence	77 (75)	.93 (.37-2,31)	.868	.67 (.3-1,51)	.336

Dependence	25 (25)	ref.		ref.	
EuroQol					
Good	54 (53)	**.37 (.16-.82)**	**.014**	**.36 (.16-.82)**	**.015**
Poor	48 (47)	ref.		ref.	

OR odds ratio, CI confidence interval, p probability of statistical significance. In bold: significant OR, CI or p-values

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Logistic regression analysis of the association between the likelihood of hospitalization or polypharmacy and nutrition status

		Likelihood of hospitalization				***Likelihood of polypharmacy***			
		Model 1 (Crude)		Model 2 (Adjust by sex and age)		Model 1 (Crude)		Model 2 (Adjust by sex and age)	
	n (%)	OR (CI95%)	p	OR (CI95%)	p	OR (CI95%)	p	OR (CI95%)	p
PREDIMED									
Medium	63 (68)	.73 (.25-2,09)	.553	.73 (.25-2,12)	.563	.92 (.31-2,68)	.875	.93 (.32-2,72)	.890
High	18 (18)	1,26 (.33-4,74)	.735	1,46 (.38-5,67)	.581	.57 (.15-2,17)	.406	.59 (.15-2,28)	.442
Poor	18 (18)	ref.		ref.		ref.		ref.	
MNA									
Normal	76 (81)	.57 (.21-1,55)	.270	.59 (.21-1,63)	.307	1,38 (.5-3,8)	.539	1,39 (.5-3,87)	.528
Risk of malnutrition	20 (40)	ref.		ref.		ref.		ref.	

OR odds ratio, CI confidence interval, p probability of statistical significance, PREDIMED PREvención con DIeta MEDiterránea, MNA Mini Nutritional Assessment. In bold: significant OR, CI or p-values.

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Supplementary Table 2. Logistic regression analysis of the association between the likelihood of hospitalization or polypharmacy and physical fitness-related polymorphisms

		Probability of hospitalization				***Probability of high medication intake***			
		Model 1 (Crude)		Model 2 (Adjusted for sex and age)		Model 1 (Crude)		Model 2 (Adjusted for sex and age)	
	n (%)	OR (CI95%)	p	OR (CI95%)	p	OR (CI95%)	p	OR (CI95%)	p
***ACTN3* (rs1815739)**									
RR+RX	79	1.32 (.49-3.53)	.582	1.38 (.51-3,75)	.53	.44 (.16-1.22)	.113	.45 (.16-1.24)	.123
XX	20	ref.		ref.		ref.		ref.	
***ECA* (In/Del)**									
II+ID	61	1.73 (.76-3,93)	.189	1.55 (.65-3.68)	.324	1,02 (.45-2.31)	.959	.93 (.39-2.22)	.869
DD	38	ref.		ref.		ref.		ref.	
***BDNF* (rs6265)**									
MetMet+MetVal	60 (42)	2.08 (.92-4.76)	.079	2.04 (.89-4.76)	.090	1.16 (.52-2,63)	.711	1.15 (.51-2.56)	.734
ValVal	39 (49)	ref.		ref.		ref.		ref.	
***PPARGC1A* (rs8192678)**									
GlyGly+GlySer	88	.55 (.15-2)	.361	.58 (.16-2.18)	.422	.78 (.22-2.74)	.696	.82 (.23-2.96)	.765
GlyGly	11	ref.		ref.		ref.		ref.	
***APOE* (rs429358/rs7412)**									
Allele 4	9	.47 (.11-1,99)	.303	.48 (.11-2.06)	.323	.84 (.21-3,33)	.801	.86 (.22-3,44)	.832
Allele 2	89	ref.		ref.		ref.		ref.	
***CKM* (rs8111989)**									
TT+TC	92	1.39 (.3-6.57)	.676	1.62 (.33-8.01)	.557	1.3 (.28-6.16)	.737	1.44 (.29-7.02)	.654
CC	7	ref.		ref.		ref.		ref.	

OR odds ratio, CI confidence interval, p probability of statistical significance. In bold: significant OR, CI or p-values