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Original article

Association between ankle-brachial index and cognitive function in participants in the PREDIMED-Plus study: cross-sectional assessment

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ABSTRACT

Introduction and objectives: The ankle-brachial index (ABI) is an indicator of peripheral artery disease (PAD). The aim of this study was to assess the association between PAD, measured with the ABI, and cognitive function in persons with overweight or obesity and metabolic syndrome.
Methods: Cross-sectional study conducted with baseline data from the PREDIMED-Plus study, which included 4898 participants (after exclusion of those without ABI measurements) aged between 55 and 75 years, and with overweight or obesity and metabolic syndrome. At the baseline assessment, we measured the ABI with a standardized protocol and assessed the presence of other cardiovascular risk factors (eg, diabetes, dyslipidemia, hypertension). Cognitive function was evaluated using several tests validated for the Spanish population (mini-mental state examination [MMSE], phonological and semantic verbal fluency test, WAIS-III working memory index [WMI], parts A and B of the trail making test (TMT), and clock drawing test). Generalized linear models were used to assess the association between the ABI and cognitive function.
Results: Among the participants, 3.4% had PAD defined as ABI $\leq$ 0.9, and 3.3% had arterial calcification defined as ABI $\geq$ 1.4. PAD was associated with age, systolic blood pressure and obesity indicators, while arterial calcification was also associated with obesity and diabetes. No significant associations were observed between cognitive function and ABI or PAD.
Conclusions: In our sample, the presence of PAD increased with age, blood pressure, and obesity. No significant association was observed between ABI, PAD, or cognitive function.
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Asociación entre índice tobillo-brazo y rendimiento cognitivo en participantes del estudio PREDIMED-Plus: estudio transversal

Palabras clave:
Enfermedad arterial periférica
Deterioro cognitivo
Índice tobillo-brazo
Estudio transversal
Síndrome metabólico

RESUMEN

Introducción y objetivos: El índice tobillo-brazo (ITB) es un indicador de enfermedad arterial periférica (EAP). El objetivo de este estudio es evaluar la asociación entre la EAP medida con el ITB y el rendimiento cognitivo de individuos con sobrepeso u obesidad y síndrome metabólico.
Métodos: Estudio transversal realizado con los datos basales del estudio PREDIMED-Plus, en el que se incluyó a un total de 4.898 participantes (tras excluir a aquellos sin medición de ITB) de entre 55 y 75 años, con sobrepeso u obesidad y síndrome metabólico. En la visita basal se midió el ITB según un protocolo estandarizado, así como otros factores de riesgo cardiovascular (diabetes mellitus, dislipemia e hipertensión arterial, entre otros). Para la evaluación del rendimiento cognitivo, se aplicaron diferentes pruebas validadas en población española (Mini-mental Test, test de fluencia verbal semántica y fonológica, test de valoración de memoria de trabajo, test del trazo y test del reloj). Para evaluar la asociación entre el ITB y el rendimiento cognitivo, se utilizaron modelos lineales generalizados.
Resultados: El 3,4% de los participantes tenían EAP, definida por un ITB $\leq$ 0,9, y un 3,3%, calcificación arterial definida por un ITB $\geq$ 1,4. La EAP se asoció con la edad, la presión arterial sistólica y los indicadores de obesidad, mientras que la calcificación arterial se asoció también con obesidad y diabetes. Entre el rendimiento cognitivo y el ITB o la EAP, no se observaron asociaciones significativas.
Conclusiones: En nuestra muestra la EAP aumenta con la edad, la presión arterial y los indicadores de obesidad. No se observa una asociación significativa entre el ITB, la EAP y el rendimiento cognitivo.
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Abbreviations

ABI: ankle-brachial index
PAD: peripheral artery disease
SBP: systolic blood pressure

INTRODUCTION

According to the World Health Organization, noncommunicable diseases and mental disorders are 2 of the greatest threats to health and development worldwide.[1]

Cognitive impairment is a public health problem with enormous social repercussions in terms of loss of quality of life and economic burden.[2] Between 5.2% and 16.3% of the Spanish population have mild cognitive impairment (MCI), but the rates for men and women older than 85 years are considerably higher, at 22% and 30%.[3] Moreover, 10% to 20% of people aged 65 years or older have signs of early MCI.[4] MCI is a slow process characterized by evident signs of cognitive decline for decades and eventual loss of independence and death.[5] The greatest challenge is thus to identify at-risk individuals who could benefit from early prevention and treatment. There is evidence that cerebrovascular disease is associated with cognitive impairment.[6] In addition, cardiovascular risk factors such as hypertension, dyslipidemia, and diabetes mellitus have been linked to both cognitive impairment and atherosclerotic disease.[7–9] Fewer studies have analyzed the link between atherosclerosis and cognitive impairment and they have reported conflicting findings.[6,10,11]

The ankle-brachial index (IBI), defined as the ratio between systolic blood pressure (SBP) in the ankle and in the brachial artery, is a predictor of cardiovascular risk.[7] The index was originally

proposed for the noninvasive diagnosis of peripheral arterial disease (PAD), but it has since been shown to be a practical, affordable, and well-received alternative for systemic atherosclerosis.[12]

A low ABI (≤ 0.9), a sign of PAD, is predictive of vascular events.[13] In terms of the association between vascular events and cognitive impairment, many observational studies,[14] though not all,[15,16] have reported an association between a low ABI and progressive cognitive impairment.[17,18]

Early assessment of cognitive function in patients with a low ABI might therefore provide useful information on susceptibility to cognitive impairment and help prevent later health problems that could affect quality of life.

The aim of this study was to evaluate the cross-sectional association between an ABI of ≤ 0.9 as an indicator of DAP and cognitive performance in older overweight or obese adults with metabolic syndrome from the PREDIMED-Plus trial.

METHODS

Study design

We performed a cross-sectional analysis of baseline data collected for participants from the PREDIMED-Plus trial with ABI measurements. The PREDIMED-Plus trial is a multicenter, parallel-group randomized cardiovascular prevention trial with a 6-year duration.[9] Participants were randomized at a ratio of 1:1 to a multifactorial weight loss intervention based on a low-calorie Mediterranean diet (adapted to individual needs), physical activity, and behavioral support or to a control group encouraged to follow a Mediterranean diet with no calorie restrictions and who received care as usual.

The trial was registered in the International Standard Randomized Controlled Trial Registry (ISRCTN89898870) in 2014. The protocol was approved by the ethics committees of the participating hospitals and the trial was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided informed consent. This cross-sectional observational study focuses on baseline data collected during the trial. None of the participants were randomized.

Participants and selection

Eligible participants were men aged 55 to 75 years and women aged 60 to 75 years who had no history of cardiovascular disease but who were overweight or obese (body mass index [BMI], 27-40 kg/m^2) and met at least 3 criteria for metabolic syndrome according to the standard definition of this condition.[19] In total, 6874 participants were recruited for the trial by 23 Spanish centers between October 2013 and December 2016. Participants without baseline ABI measurements were excluded from the current study; most of these (n = 1871) were from centers that did not measure this index. Another 105 patients were excluded because of missing data on education. The final sample (n = 4898) yielded a statistical power of more than 80% to detect significant differences of at least 10% in cognitive test performance. The data collected for our analyses corresponded to the data in the PREDIMED-PLUS database on August 10, 2017.

Ankle-brachial index

PAD was evaluated using the ABI and defined using a cutoff value of 0.9. All ABI measurements were made by trained nursing staff after the individual had been at rest in a supine decubitus position (45°) for at least 5 minutes in a quiet environment. SBP was measured at the brachial artery in both arms and at the pedal and posterior tibial arteries in both ankles using a sphygmomanometer cuff and an 8-MHz vascular Doppler probe (TRISMED, model DP6000). The index was calculated as the ratio between the highest pressure for each ankle (numerator) and the highest pressure for each arm (denominator). The lower of the indices calculated for 2 two sides of the body was established as the definitive ABI. Individuals were classified into 4 ABI categories: low (ABI ≤ 0.9, indicating DAP), high (ABI ≥ 1.4, indicating arterial calcification [noncompressible artery]),[7] normal (ABI > 0.9 to < 1.2), and normal with a risk of arterial calcification (ABI ≥ 1.2 to < 1.4).[20]

Cognitive tests

Cognitive performance was analyzed using neuropsychological tests that have proven useful for detecting early cognitive impairment or monitoring the progression of dementia.[21] The following tests were used:

- The Mini-Mental State Exam, which tests cognitive function and is used to screen for dementia and monitor its progress.[22] The total possible score ranges from 0 to 30. A score of less than 24 indicates cognitive impairment and has been linked to a diagnosis of dementia in 79% of cases.[23] The test has a specificity of 80% to 100%.[6]
- The Semantic and Phonemic Verbal Fluency tests, which assess mental flexibility, processing speed, and language. Individuals are given 1 minute to repeat as many words as possible from a given semantic category or starting with a given letter.[21] In the PREDIMED-Plus trial, semantic verbal fluency was measured using the animals category, while phonemic verbal fluency was measured using words starting with the letter *P*.[24] The total possible score ranges from 0 to 40.[25]
- The verbal and visual working memory digit span subtest of the WAIS-III,[26] which evaluates cognitive abilities such as attention, resistance to distraction, immediate auditory memory, and working memory.[27] In this test, individuals are read a series of digits and asked to repeat them in order (forward span) and reverse order (backward span).
- The Trail Making Test, which tests visual scanning ability, graphomotor speed, and executive function and is used to assess brain dysfunction.[28] The test consists of 2 parts. In part A, individuals are asked to draw a line connecting, in sequential order, a series of 25 numbers randomly positioned in circles on a sheet of paper. In Part B, they are asked to alternate, also in sequential order, between numbers (1-12) and letters (A-I). The score is determined by the time it takes the individual to complete each task (maximum 300 seconds).
- The clock-drawing test, which is used to assess cognitive function and is an indicator of dementia (Alzheimer disease in particular).[29] The test consists of drawing the hours 1 to 12 in a circle resembling a clock and then drawing the hands of the clock to indicate a given time.

Covariates

A general questionnaire was used to obtain information on sociodemographic variables, including smoking, the presence of clinical diseases such as diabetes mellitus, use of medication, and family history of disease. Anthropometric variables were obtained by trained staff (nurses and dieticians-nutritionists) in accordance with the PREDIMED-Plus protocol. Weight was measured using

high-precision electronic calibrated weighing scales, and height using a wall-mounted stadiometer. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured halfway between the last rib and the iliac crest using an anthropometric measuring tape. All anthropometric variables were obtained in duplicate.

Blood pressure was measured in triplicate (with readings taken 5 minutes apart while the individual was seated) using a validated semiautomatic oscillometer (GE V100 vital signs monitor). Individuals were considered to be hypertensive when the mean of the 3 SBP measurements was higher than 135 mmHg, when their diastolic blood pressure was higher than 85 mmHg, or when they were on antihypertensive drugs.

Blood samples were collected after a fasting period of at least 8 hours. Biochemical parameters (fasting plasma glucose levels, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides) were measured in local laboratories using standard methods. Individuals were considered to be diabetic when they had a confirmed diagnosis by standard methods or when they reported being on medication to treat high plasma glucose levels.

Statistical analysis

Quantitative variables are expressed as mean ± SD and qualitative variables as numbers and percentages. Between-group differences were analyzed using the *t* test and analysis of variance for quantitative variables and the chi-square test for qualitative variables. Generalized linear models were used to evaluate associations between cognitive performance on the different neuropsychological tests and ABI as both a continuous variable and a categorical variable with 4 levels (≤ 0.9, > 0.9 to < 1.2 [reference category], ≥ 1.2 to < 1.4, and ≥ 1.4). An initial model was adjusted for sociodemographic variables (age, sex, years of education), while a second model was adjusted for major cardiovascular risk factors (diabetes, waist circumference, and PAD). Generalized linear models are used to calculate effect size (ηp^2), which provides an estimate of the percentage of variance explained by the variables in each analysis. The analyses were repeated with 2 of the ABI categories (≤ 0.9 and > 0.9 to 1.4, the reference category) and exclusion of the high ABI category (≥ 1.4). A sensitivity analysis stratified by sex and age (< 70 vs ≥ 70 years) was performed for all models.

Differences with a *P* level of less than .05 were considered significant. Statistical analyses were performed in SPSS v23.

RESULTS

Of the 4898 people included in this cross-sectional study, 166 had an ABI of ≤ 0.9 (PAD), 1266 had an ABI of ≥ 1.2 to < 1.4 (risk of calcification), and 159 had an ABI of ≥ 1.4 (arterial calcification).

The baseline characteristics of the individuals, shown by ABI category, are summarized in table 1. Individuals with an ABI of ≤ 0.9 were older, more likely to be female, and had a higher SBP

Table 1
Baseline characteristics of participants in PREDIMED-Plus trial according to ABI category

	ABI category				
Characteristics (*n* = 4898)	Low, ABI ≤ 0.9 (n = 166)	Normal, ABI > 0.9 to < 1.2 (n = 3466)	Normal-high, ABI ≥ 1.2 to < 1.4 (n = 1107)	HIgh, ABI ≥ 1.4 (n = 159)	*P**
Age, y	65.3 ± 4.8	65.0 ± 5.0	64.6 ± 5.0	64.5 ± 5.0	.046
Female sex	87 (52.4)	1.774 (51.2)	433 (39.1)	54 (34.2)	.001
Education, y	11.2 ± 5.3	11.4 ± 5.4	11.6 ± 5.6	11.0 ± 5.6	.350
Smoking history (n = 4878)					.135
Smoker	29 (17.6)	455 (13.2)	142 (12.9)	18 (11.5)	
Former smoker	71 (43.2)	1.462 (42.3)	513 (46.5)	69 (43.9)	
Never smoker	65 (39.4)	1.536 (44.5)	448 (40.6)	70 (44.6)	
Systolic blood pressure, mmHg	143.1 ± 19.8	137.7 ± 17.1	136.2 ± 17.0	137.4 ± 17.3	.001
Diastolic blood pressure, mmHg	80.5 ± 10.7	80.5 ± 9.9	80.1 ± 10.3	81.2 ± 10.7	.564
Hypertension	149 (89.8)	3.180 (91.7)	1.000 (90.8)	143 (89.9)	.385
Baseline glucose, mg/dL	114.7 ± 37.6	112.3 ± 29.2	112.6 ± 28.0	116.5 ± 29.3	.170
HbA_{1c}, %	6.1 ± 1.0	6.1 ± 0.9	6.1 ± 0.9	6.1 ± 0.8	.587
Diabetes mellitus	39 (23.5)	832 (24.0)	285 (25.7)	50 (31.4)	.135
HDL-C, mg/dL	45.8 ± 11.9	47.5 ± 11.7	46.9 ± 11.4	47.3 ± 11.0	.130
Triglycerides, mg/dL	157.6 ± 84.9	151.4 ± 79.1	153.7 ± 81.2	147.9 ± 66.0	.697
Body mass index, kg/m^2	33.3 ± 3.5	32.5 ± 3.4	32.6 ± 3.5	33.1 ± 3.6	.001
Waist circumference, cm	108.9 ± 9.6	107.5 ± 9.6	108.5 ± 9.8	109.6 ± 9.5	.001
MMSE (n = 4558)	28.23 ± 1.97	28.18 ± 1.98	28.30 ± 1.82	28.19 ± 2.00	.405
Phonemic verbal fluency (n = 4854)	12.3 ± 5.1	12.1 ± 4.5	12.1 ± 4.5	12.9 ± 4.9	.208
Semantic verbal fluency (n = 4854)	16.6 ± 4.8	16.1 ± 4.9	16.0 ± 4.7	16.5 ± 5.3	.449
Working memory (n = 3351)	13.8 ± 4.0	13.6 ± 4.1	14.0 ± 4.1	13.4 ± 4.2	.075
Trail Making Test (n = 4683)	182.3 ± 84.0	187.5 ± 97.2	177.8 ± 90.2	177.8 ± 95.6	.025
Clock drawing test (n = 4554)	5.8 ± 1.3	6.0 ± 1.3	5.9 ± 1.2	5.8 ± 1.5	.714

ABI, ankle-brachial index; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination.
Values are expressed as No. (%) mean ± standard deviation.
* *P* values obtained by analysis of variance for quantitative variables and the chi-square test for qualitative variables.

Table 2
Association between ABI categories and cognitive performance on different neuropsychological tests

ABI	MMSE			Phonemic verbal fluency			Semantic verbal fluency			Working memory			*Trail Making Test*			Clock-drawing test		
	β	η_p^2	*P*	β	η_p^2	*P*	β	η_p^2	*P*	β	η_p^2	*P*	β	η_p^2	*P*	β	η_p^2	*P*
ABI ≤ 0.9	0.009	< 0.001	.951	0.257	< 0.001	.437	0.621	0.001	.083	0.280	< 0.001	.412	−7.012	< 0.001	.300	−0.092	< 0.001	.351
ABI > 0.9 to < 1.2	0 (ref)			0 (ref)			0 (ref)			0 (ref)			0 (ref)			0 (ref)		
ABI ≥ 1.2 to < 1.4	0.057	< 0.001	.384	−0.165	< 0.001	.251	−0.339	0.001	.030	0.216	0.001	.158	−2.662	< 0.001	.364	−0.008	< 0.001	.853
ABI ≥ 1.4	0.017	< 0.001	.913	0.800	0.001	.018	0.267	< 0.001	.466	−0.280	< 0.001	.416	−4.684	< 0.001	.494	−0.069	< 0.001	.495

ABI, ankle-brachial index; MMSE, mini-mental state examination; ref, reference category.
Generalized linear model adjusted for age, sex, and years of education.
β indicates the change in cognitive performance on each neuropsychological test for each ABI category (with normal ABI as the reference category). η_p^2 indicates effect size.

and BMI. Those with an ABI of ≥ 1.4 were more likely to be diabetic. The only significant difference observed between the groups for cognitive performance was for the Trail Making Test, with individuals with a normal ABI scoring higher.

Associations between ABI categories (with normal ABI [> 0.9 to < 1.2] as the reference category) and cognitive performance on the different neuropyschological tests are shown in table 2. In the models adjusted for age, sex, and level of educational, individuals with PAD (ABI ≤ 0.9) did not score differently on any of the tests. Differences were observed for semantic verbal fluency (β = 0.339, *P* = .030) between individuals with a normal ABI (> 0.9 to < 1.2) and those with a normal ABI but risk of calcification (≥ 1.2 to < 1.4) and for phonemic verbal fluency (β = .800, *P* = .018) between individuals with a normal ABI and those with an ABI of ≥ 1.4 (arterial calcification). The models containing just 2 ABI categories (≤ 0.9 indicating PAD and the reference category > 0.9 to < 1.4) showed no significant differences in cognitive performance (table 1 of the supplementary data). The differences were also nonsignificant for the models featuring ABI as a continuous variable (data not shown).

The results after adjustment of the models for the cardiovascular risk factors SBP, waist circumference, and diabetes are shown in table 3. The findings were similar, with significant associations observed in the ABI categories ≥ 1.2 to < 1.4 and ≥ 1.4. On analyzing the combined categories of normal and normal-high ABI (with exclusion of individuals with high ABI), we observed no differences in cognitive performance compared with individuals with a low ABI (table 2 of the supplementary data).

Similar results were observed in the sensitivity analyses with stratification by sex and age (≥ 70 vs < 70 years), as no associations were detected between PAD and cognitive performance in any of the subgroups (data not shown).

DISCUSSION

In this cross-sectional study of a large sample of older overweight or obese adults with metabolic syndrome from the PREDIMED-Plus trial, a low ABI as an indicator of PAD was not associated with cognitive performance on the different neuropsychological tests performed. While we did observe a number of significant associations for individuals with a high ABI (arterial calcification), there was no evidence of any clinically relevant trends, and therefore our findings might be the result of chance.

The association between PAD assessed by ABI and cognitive function remains a topic of debate, with the literature showing contradictory results. Several studies have reported an association between a low ABI and cognitive performance. In a study of individuals aged 70 to 89 years with impaired physical mobility, Espeland et al.[12] reported a significant association between a low ABI and cognitive performance assessed using an extensive series of tests; they also found that a low ABI predicted MCI at 2-years of follow-up. They did not, however, find any association between changes in ABI and cognitive performance during this period, probably because a longer follow-up would be needed to detect changes in cognitive function. Similar findings were reported by Johnson et al.,[16] who detected an association between the ABI and cognitive performance (evaluated using similar tests to us) at baseline but not between changes in the ABI and better or worse cognitive function at 5 and 12 years. In that study, the follow-up period was long, but the sample was smaller (n = 717). In another study of 918 individuals analyzed in 2 waves (mean ages, 73 and 87 years), Laukka et al., [30] observed a significant association between a high ABI and better cognitive performance, but not between DAP indicators and worse cognitive function. Wang et al.[6] also observed an association between a low ABI and cognitive

Table 3
Association between ABI categories, cardiovascular risk factors, and cognitive performance assessed by different neuropsychological tests

	MMSE			Phonemic verbal fluency			Semantic verbal fluency			Working memory			*Trail Making Test*			Clock-drawing test		
	β	η_p^2	*P*	β	η_p^2	*P*	β	η_p^2	*P*	β	*P*	β	η_p^2	*P*	β	η_p^2	p
ABI																		
ABI ≤ 0.9	0.013	< 0.001	.929	0.293	< 0.001	.380	0.645	0.001	.075	0.333	< 0.001	.336	−0.741	< 0.001	.280	−0.093	< 0.001	.344
ABI >0.9 to < 1.2	0 (ref)			0 (ref)			0 (ref)			0 (ref)			0 (ref)			0 (ref)		
ABI ≥ 1.2 to < 1.4	0.061	< 0.001	.352	−0.191	< 0.001	.201	−0.385	0.001	.017	0.191	< 0.001	.232	−3.311	< 0.001	.277	−0.006	< 0.001	.888
ABI ≥ 1.4	0.032	< 0.001	.833	0.899	0.001	.013	0.438	< 0.001	.261	−0.090	< 0.001	.810	−6.507	< 0.001	.373	−0.069	< 0.001	.498
SBP, mmHg	−0.001	< 0.001	.532	−0.003	< 0.001	.424	−0.003	< 0.001	.399	−0.001	< 0.001	.749	−0.098	< 0.001	.184	−0.001	< 0.001	.617
Waist circumference, cm	−0.003	< 0.001	.274	−0.005	< 0.001	.0494	0.008	< 0.001	.307	−0.011	0.001	.124	0.442	< 0.002	.001	0.001	< 0.001	.473
Diabetes (yes)	−0.255	0.004	< .001	−0.620	0.004	< .001	−0.631	0.004	< .001	−0.060	< 0.001	.371	13.246	0.005	< .001	−0.057	< 0.001	.174

ABI, ankle-brachial index; MMSE, mini-mental state examination; ref, reference category; SBP, systolic blood pressure.
Generalized linear model adjusted for age, sex, and years of education. β indicates change in cognitive performance on each of the neuropsychological tests for each ABI category (with normal ABI as the reference category) and the corresponding changes associated with an increase of 1 mmHg for SBP and 1 cm for waist circumference and presence vs absence of diabetes. η_p^2 indicates effect size.

performance that was independent of other cardiovascular risk factors. The association was stronger in nonhypertensive and diabetic patients.

As hypothesized by other authors,[31] arterial stiffness may be predictive of cognitive impairment, but it has not yet been determined whether the association is a cause-effect association or simply the result of confounders such as age, hypertension, and diabetes, each associated with arterial stiffness and cognitive performance. In our study, the association between ABI and cognitive performance after adjustment for these factors was nonexistent. Of the various cardiovascular risk factors analyzed, diabetes was most strongly associated with performance on the different neuropsychological tests, supporting previous findings for this cohort.[32]

Our study has some limitations. First, our findings are based on a cross-sectional analysis. Nonetheless, cross-sectional data should show an association between DAP and cognitive performance if such an association existed. It is possible, however, that PAD precedes cognitive impairment, and this is relevant in our cohort, where the individuals were not particularly old. Longitudinal studies of older individuals might thus detect an association between DAP and cognitive impairment. Cross-sectional studies are also limited by the risk of bias due to reverse causality whereby it is impossible to determine whether the cause (in this case PAD) precedes the effect (cognitive impairment). Second, all our patients had metabolic syndrome and many of them were hypertensive. We may not, therefore, have detected an association between PAD and cognitive impairment because the population was not sufficiently heterogeneous in terms of the other variables analyzed. The homogeneity of the population (adults with metabolic syndrome) also means that our results cannot be extrapolated to the general population. In addition, the inclusion of overweight and obese individuals could limit the usefulness of ABI as an indicator of PAD, although previous studies have not found overweight and obesity to be limiting factors for the calculation of the ABI.[33,34] Whatever the case, with a sample as large as ours, we should have detected some degree of association had it existed. Finally, because ABI is not an objective measure of PAD, the possibility of bias cannot be completely ruled out. Nonetheless, our calculations were based on measurements obtained by trained personnel following a standardized protocol. Similarly, we were unable to confirm that individuals with an ABI of > 1.4 had arterial calcification, as imaging tests were not performed. That said, guidelines report an association between a high ABI and arterial calcification.

Our study also has some strengths, including its large sample size, the comparable age and cardiovascular risk profile of the participants, the use of a standardized protocol to obtain the study variables, the adjustment for possible confounders in the different statistical analyses, and the performance of sensitivity analyses.

CONCLUSIONS

The results of this cross-sectional study of a large sample of overweight or obese participants with metabolic syndrome showed no association between ABI and cognitive performance. DAP, however, may precede cognitive impairment, meaning that such an association might not be so easy to detect in a younger population such as ours. Assuming that DAP does precede cognitive impairment, it would be advisable to target patients with peripheral vascular disease in this age group to prevent cognitive impairment. Accordingly, and considering the limitations of cross-sectional studies, it is imperative to conduct longitudinal studies to confirm or reject our findings.

WHAT IS KNOWN ABOUT THE TOPIC?

- A low ABI, which is an indicator of PAD, is predictive of vascular events. In addition, several observational studies have reported a link between a low ABI and progressive cognitive decline. Early assessment of cognitive function in patients with a low ABI might provide useful information on susceptibility to cognitive impairment and help prevent later health problems that could affect quality of life.

WHAT DOES THIS STUDY ADD?

- We investigated the cross-sectional association between the ABI as a measure of PAD and cognitive performance in older overweight or obese adults with metabolic syndrome from the PREDIMED-Plus trial. A low ABI, indicating PAD, was associated with age, SBP, and indicators of obesity, but not with cognitive performance assessed using different tests after adjustment for confounders. Further longitudinal studies are necessary to confirm our findings.

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CONFLICTS OF INTEREST

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APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2020.06.041

REFERENCES

1. Organización Mundial de la Salud. *Es hora de actuar: informe de la Comisión independiente de alto nivel de la OMS sobre enfermedades no transmisibles.* 2018. Available at: http://apps.who.int/iris/bitstream/handle/10665/272712/9789243514161-spa.pdf?ua=1. Accessed 13 May 2020
2. Bos D, Vernooij MW, de Bruijn RFAG, et al. Atherosclerotic calcification is related to a higher risk of dementia and cognitive decline. *Alzheimers Dement.* 2015;11:639–647.
3. Bermejo Pareja F, Benito León J, Vega QAV, et al. La cohorte de ancianos NEDICES Metodología y principales hallazgos neurológicos. *Rev Neurol.* 2008;46:416–423.
4. Petersen RC. Clinical practice Mild cognitive impairment. *N Engl J Med.* 2011;364:2227–2234.
5. Perna L, Wahl HW, Mons U, Saum KU, Holleczek B, Brenner H. Cognitive impairment, all-cause and cause-specific mortality among non-demented older adults. *Age Ageing.* 2015;44:445–451.
6. Wang A, Jiang R, Su Z, et al. A low ankle-brachial index is associated with cognitive impairment: The APAC study. *Atherosclerosis.* 2016;255:90–95.
7. Aboyans A, del G, de TV, Ricco JB, Bartelink MLEL, et al. Guía ESC. 2017 sobre el diagnóstico y tratamiento de la enfermedad arterial periférica, desarrollada en colaboración con la European Society for Vascular Surgery (ESVS). *Rev Esp Cardiol.* 2018;71:111e1-e69.
8. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg.* 2007;45SupplS:S5–S67.
9. Martínez-González MA, Buil-Cosiales P, Corella D, et al. Cohort profile: Design and methods of the PREDIMED-Plus randomized trial. *Int J Epidemiol.* 2019;48:387–388.
10. Johnson W, Price JF, Rafnsson SB, Deary IJ, Fowkes FGR. Ankle-brachial index predicts level of, but not change in, cognitive function: the Edinburgh Artery Study at the 15-year follow-up. *Vasc Med.* 2010;15:91–97.
11. Rossetti HC, Weiner M, Hynan LS, Cullum CM, Khera A, Lacritz LH. Subclinical atherosclerosis and subsequent cognitive function. *Atherosclerosis.* 2015;241:36–41.

12. Espeland MA, Newman AB, Sink K, et al. Associations between ankle-brachial index and cognitive function: results from the Lifestyle Interventions and Independence for Elders Trial. *J Am Med Dir Assoc.* 2015;16:682–689.
13. Aboyans V, Criqui MH, Abraham P, et al. Measurement and interpretation of the Ankle-Brachial Index: A scientific statement from the American Heart Association. *Circulation.* 2012;126:2890–2909.
14. Van Oijen M, De Jong FJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Atherosclerosis and risk for dementia. *Ann Neurol.* 2007;61:403–410.
15. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the cardiovascular health study. *Circulation.* 1993;88:837–845.
16. Johnson W, Price JF, Rafnsson SB, Deary IJ, Fowkes FG. Ankleg-brachial index predicts level of, but not change in, cognitive function: The Edinburgh Artery Study at the 15-year follow-up. *Vasc Med.* 2010;15:91–97.
17. Li X, Lyu P, Ren Y, An J, Dong Y. Arterial stiffness and cognitive impairment. *J Neurol Sci.* 2017;380:1–10.
18. Price JF, McDowell S, Whiteman MC, Deary IJ, Stewart MC, Fowkes FG. Ankle brachial index as a predictor of cognitive impairment in the general population: ten-year follow-up of the Edinburgh Artery Study. *J Am Geriatr Soc.* 2006;54:763–769.
19. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart Lung, and Blood Institute; American Heart Association; World Heart Federation; International. *Circulation.* 2009;120:1640–1645.
20. Lahoz C, Mostaza JM. Ankle-brachial index: a useful tool for stratifying cardiovascular risk. *Rev Esp Cardiol.* 2006;59:647–649.
21. Delgado C, Salinas P. Evaluación de las alteraciones cognitivas en adultos mayores. *Rev Hosp Clín Univ Chile.* 2009;20:244–251.
22. Folstein MF, Folstein SEMP. Mini-mental state. A grading the cognitive state of patiens for the clinician. *J Psychiatr Res.* 1975;12:189–198.
23. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *J Psychiatr Res.* 2009;43:411–431.
24. Van Der Elst W, Van Boxtel MPJ, Van Breukelen GJP, Jolles J. Normative data for the Animal Profession and Letter M Naming verbal fluency tests for Dutch speaking participants and the effects of age, education, and sex. *J Int Neuropsychol Soc.* 2006;12:80–89.
25. Horcajuelo C, Criado-Álvarez JJ, Correa S, Romo C, Horcajuelo C, Correa S. Análisis de tareas de fluidez verbal semántica en personas diagnosticadas de la enfermedad de Alzheimer y adultos sanos. *Rev Invest Logopedia.* 2018. Available at: https://www.redalyc.org/pdf/3508/350833943002.pdf. Accessed 13 May 2020
26. Funes CM, Hernández Rodriguez J, Lopez SR. Norm comparisons of the Spanish-language and English-language WAIS-III: Implications for clinical assessment and test adaptation. *Psychol Assess.* 2016;28:1709–1715.
27. Wechsler D. Test de inteligencia de Wechsler para adultos-IV (WAIS-IV). *Buenos Aires: Paidós;.* 2013;1–21.
28. Llinàs-Reglà J, Vilalta-Franch J, López-Pousa S, Calvó-Perxas L, Torrents Rodas D, Garre-Olmo J. The Trail Making Test. *Assessment.* 2017;24:183–196.
29. Spenciere B, Alves H, Charchat-Fichman H. Sistemas de pontuação do teste do desenho do relãgio: Uma revisão histórica. *Dement e Neuropsychol.* 2017;11:6–14.
30. Laukka EJ, Starr JM, Deary IJ. Lower Ankle-Brachial index is related to worse cognitive performance in old age. *Neuropsychology.* 2014;28:281–289.
31. Iulita MF, Noriega de la Colina A, Girouard H. Arterial stiffness, cognitive impairment and dementia: confounding factor or real risk? *J Neurochem.* 2018;144:527–548.
32. Mallorquí-Bagué N, Lozano-Madrid M, Toledo E, et al. Type 2 diabetes and cognitive impairment in an older population with overweight or obesity and metabolic syndrome: baseline cross-sectional analysis of the PREDIMED-Plus study. *Sci Rep.* 2018;8:16128.
33. Zhang Y, Chen J, Zhang K, et al. Inflammation and oxidative stress are associated with the prevalence of high aankle-brachial index in metabolic syndrome patients without chronic renal failure. *Int J Med Sci.* 2013;10:183–190.
34. Tapp RJ, Balkau B, Shaw JE, Valensi P, Cailleau M, Eschwege E. Association of glucose metabolism, smoking and cardiovascular risk factors with incident peripheral arterial disease: The DESIR study. *Atherosclerosis.* 2007;190:84–89.