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Research Article

Physical Fitness is a Mediator in the Relationship between Arterial Stiffness and Cognitive Function

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ABSTRACT

Background: To investigate physical fitness as a mediator of the relationship between arterial stiffness and cognitive function in seniors.

Methods: This is a cross-sectional study comprising 155 individuals free from chronic diseases (75.5 ± 6.5 years; 69.7% female). Carotid-femoral pulse wave was assessed through applanation tonometry. Cognitive function was evaluated with Montreal Cognitive Assessment (MoCA). Physical fitness was assessed through handgrip strength and Senior Fitness Test (SFT). A *Z*-score including individual physical fitness components was computed as a global index of physical fitness. Hayes's PROCESS macro for Statistical Package for the Social Sciences was used for the simple mediation analysis, using bootstrapped procedures.

Results: After adjustments for sex and age, physical fitness *Z*-score mediated the relationship between arterial stiffness and cognitive function [Indirect effect = −0.382 (95% CI −0.670 to −0.138)].

Conclusion: Findings suggest that physical fitness, independently of sex and age, is a mediator on the relationship between arterial stiffness and cognitive function in seniors free from chronic diseases.

1. INTRODUCTION

The demographic ageing is an actual phenomenon with deep implications in society [1]. Together with ageing, conditions such as cognitive impairment are rapidly increasing [2]. Because until now there is no cure for dementia, any positive strategy adopted in terms of prevention and/or delay its onset, might be helpful.

Primary aging together with the aggregation of other cardiovascular risk factors lead to an increase in arterial stiffness [3,4], which in its turn is related to a reduced capacity to cushion the pulsatile flow and to downgrade blood pressure [5,6]. As a result, end organs such the brain are continuously and repeatedly supplied by an aggressive blood flow pattern, leading to long-term micro vascular damage, related with cognitive impairment [4,6].

There are evidences showing that Pulse Wave Velocity (PWV) is associated with white matter hyper-intensities, believed to reflect predominantly cerebral small vessel disease [7]. Indeed, aortic stiffness was showed to be associated with white matter hyper-intensity and smaller total brain volume [4,6,7].

Physical fitness is a set of attributes that are health or skill related, and reflects the level of ability to perform daily life activities [8]. Physical fitness depends on genetics, but it is largely influenced by the amount of physical activity that human beings adopt along life [8]. There are evidences showing that physical fitness is an independent predictor of all-cause mortality and cardiovascular events [9]. Data from cross-sectional and longitudinal studies demonstrates a negative association between arterial stiffness and physical fitness [10,11] and a positive association between cognitive function and physical fitness [12,13].

Despite these evidences, there is still unknown whether physical fitness mediates the association between arterial stiffness and cognitive function. The purpose of this study is to investigate the role of physical fitness as a mediator of the relationship between arterial stiffness and cognitive function in seniors free from chronic diseases.

2. MATERIALS AND METHODS

2.1. Study Design and Participants

This is a cross-sectional study comprising 155 individuals (75.5 ± 6.5 years; 69.7% female). Participants were invited from daily-care institutions and senior physical activity programs from Porto – Portugal. The inclusion criterion was age ≥ 65 years old. Exclusion criteria were: (i) established diagnosis of cardiovascular disease, (ii) severe cognitive disorders, (iii) orthopedic impairments, (iv) arrhythmias, (v) severe hypertension [systolic blood pressure (SBP) > 180 mmHg or diastolic blood pressure (DBP) > 100 mmHg], (vi) acute coronary syndrome, (vii) pulmonary and renal comorbidities, and (viii) peripheral arterial disease.

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Data availability statement: Data available on request due to privacy/ethical restrictions.

The protocol was approved by the ethics board of the Faculty of Sports, University of Porto (24th March 2018; Number: CEFADE 02.2018). All participants signed the informed consent form and all procedures were conducted in full accordance with Helsinki Declaration.

2.2. Data Collection

Two appointments with 7 days interval were necessary to perform all assessments. In the first one, participants were screened for eligibility criteria, sociodemographics, pre-existing clinical conditions, and regular medication. In the same appointment, participants were assessed for physical fitness and accelerometers were delivery. Seven days after, participants return to the lab to be assessed for cognition, regional arterial stiffness and to return the accelerometers.

2.3. Anthropometrics

Weight (kg) and height (m) were assessed using a scale (Tanita, Innerscan BF-522W, Japan) and a standard wall-mounted stadiometer (SECA 213, Hamburg, Germany), respectively. Body Mass Index (BMI, kg/m^2) was calculated as ratio of weight to squared height. Waist circumference (cm) was measured with a flexible tape at the midpoint between the lowest rib and iliac crest. Hip circumference (cm) was measured at the maximum diameter.

2.4. Physical Fitness

Physical fitness was assessed with Senior Fitness Test (SFT) [14]. The battery comprises the 6-min walk test to estimate cardiorespiratory fitness; the 8-foot up and go test, to assess agility and dynamic balance; the 30-s arm-curl test and the 30-s sit-to-stand test to quantify upper- and lower-body strength, respectively; sit and reach and back scratch tests to measure lower- and upper-body flexibility, respectively. In addition, a digital handgrip dynamometer (Jamar Plus+, Fabrication Enterprises Inc., Bolingbrook, Illinois, USA) was used to evaluate upper-body isometric strength. Measurements were taken with the participant in the seated position, with elbow flexed at 90° and the forearm and wrist in neutral position. Three maximal attempts lasting 3 s were made on each arm alternately, with 1 min resting between attempts. The result was the average between the three measurement of each arm [15].

2.5. Blood Pressure and Arterial Stiffness

All assessment were made at rest in a quiet, semi-dark room with an average temperature of 21°C.

A single trained researcher performed blood pressure and arterial stiffness measurements after 20 min resting in supine position. Blood pressure was assessed by a digital sphygmomanometer (Colin, BP 8 800, Critikron Inc., Komaki City, Japan) on the left arm and SBP and DBP were computed as the average of the three readings. Additional readings were performed when differences between readings exceeded 5 mmHg. From the SBP and DBP, the Pulse Pressure (PP) and Mean Blood Pressure (MBP) were calculated [16].

Arterial stiffness was measured by Carotid-Femoral PWV (cfPWV), using an applanation tonometry device (SphygmoCor, AtCor Medical, Sydney, Australia), according to international guidelines [16]. The direct distance between carotid and femoral pulses was used. Two valid measures were performed and average was used for analysis. The final result was corrected by 0.8 [17].

2.6. Cognitive Function

The Portuguese version of the Montreal Cognitive Assessment (MoCA) [18] was used to evaluate a variety of cognitive disorders. This questionnaire evaluates executive functions, language, visuospatial abilities, short-term memory, attention, concentration and working memory, spatial and temporal orientation domains. The test has a maximum score of 30 points. Result ≥26 points is related with normal cognitive function. One point was assigned to the total final score of participants with 12 or less years of education [19].

2.7. Statistical Analysis

Statistical normality was verified through skewness and kurtosis [20]. The continuous variables were expressed as mean ± standard deviation and frequency distribution for categorical data. Comparisons between male and females were performed using the independent *t*-test and Chi-square as appropriate. A *Z*-score including all physical fitness components was computed as a global index of physical fitness. For the mediation analysis, the simple mediation model with non-standard regression coefficients and the bootstrapping method proposed by Hayes [21] was used. There were computed 5000 bootstrapping simulations for each model in order to derive total, direct and indirect effects. Mediation was assumed when the confidence interval of the indirect effect did not contain zero. Mediation analysis was performed through the PROCESS macro v.3.0 (Columbos, Ohio, USA) for Statistical Package for the Social Sciences (SPSS). Mediation analyzes were adjusted for sex and age.

Data were analyzed using SPSS (IBM v.24.0, Chicago, IL, USA) and a value of $p < 0.05$ was considered statistically significant.

3. RESULTS

Physical characteristics, education, risk factors, habitual medication, hemodynamics and physical fitness components are depict in Table 1. Comparisons between genders showed that male had higher waist circumference compared to female (102.3 ± 14.8; 91.2 ± 11.9, $p < 0.001$, respectively). The distribution across education categories was significantly different between genders ($p = 0.014$). There were significant differences in hemodynamics variables. Compared with males, females presented lower DBP (70.8 ± 6.1; 66.3 ± 9.8, $p < 0.001$, respectively) and higher resting heart rate (59.3 ± 9.3; 65.4 ± 9.5, $p < 0.001$, respectively). Significant differences were also observed between genders for single physical fitness parameters and global *Z*-score of physical fitness with males presenting higher means compared with females (Table 1). Finally, male (22.0 ± 4.7 score) had a significantly superior score than females (19.2 ± 6.7 score) in the cognitive assessment.

Table 1 Sample characteristics

	Total (n = 155)	Female (n = 108)	Male (n = 47)	p-value
Physical characteristics, mean ± SD				
Age (years)	75.5 ± 6.5	75.8 ± 6.6	74.8 ± 6.5	0.384
Body mass index (kg/m^2)	27.6 ± 4.4	27.5 ± 4.6	27.7 ± 4.0	0.873
Waist circumference (cm)	94.6 ± 13.8	91.2 ± 11.9	102.3 ± 14.8	<0.001
Hip circumference (cm)	103.2 ±14.8	101.9 ± 10.2	106.3 ± 21.8	0.781
Education, N (%)				
Primary and elementary education	69 (107)	74 (80)	57.4 (27)	0.014
Secondary school	18.7 (29)	13 (14)	31.8 (15)	
Higher education	12.3 (19)	13 (14)	10.6 (5)	
Risk factors, %				
Current smoker	2.2	1.1	4.5	0.241
Hypertension	55.1	53.3	59.1	0.522
Type II diabetes	16.9	18.5	13.6	0.481
Dyslipidemia	44.3	45.5	41.9	0.697
Obesity	26.5	26.9	25.5	0.864
Medications, %				
Antihypertensive	66.3	59.3	80.0	0.051
Lipid-lowering	46.1	49.2	40.0	0.413
Oral anti-diabetic	13.5	11.9	16.7	0.531
Antidepressant	14.6	16.9	10.0	0.380
Anxiolytic	22.5	25.4	16.7	0.349
Antiplatelet agents	28.1	27.1	30.0	0.775
Hemodynamics, mean ± SD				
SBP (mmHg)	128.1 ± 17.1	127.4 ± 19.0	129.7 ± 11.9	0.367
DBP (mmHg)	67.7 ± 9.0	66.3 ± 9.8	70.8 ± 6.1	0.001
Mean arterial pressure (mmHg)	88.9 ± 11.7	88.2 ± 13.2	90.6 ± 7.5	0.143
Pulse pressure (mmHg)	59.9 ± 12.9	60.8 ± 13.8	58.1 ± 10.6	0.236
Heart Rate (bpm)	63.5 ± 9.9	65.4 ± 9.5	59.3 ± 9.3	<0.001
cfPWV (m/s)	11.5 ± 3.1	11.7 ± 3.3	11.0 ± 2.6	0.199
Physical fitness, mean ± SD				
Lower-body strength (reps)	17.0 ± 5.9	16.1 ± 5.9	18.9 ± 5.5	0.008
Upper-body strength (reps)	18.0 ± 6.2	16.9 ± 6.2	20.6 ± 5.6	0.001
Lower-body flexibility (reps)	−8.4 ± 13.0	−8.4 ± 12.5	−8.6 ± 14.2	0.918
Upper-body flexibility (cm)	−18.9 ± 12.8	−18.0 ± 12.4	−21.1 ± 13.7	0.179
Agility/dynamic balance (s)	7.2 ± 4.9	7.9 ± 5.5	5.6 ± 2.9	0.001
Cardiorespiratory fitness (m)	471.3 ± 161.7	438.2 ± 159.5	545.2 ± 142.2	<0.001
Handgrip strength (kgf)	21.7 ± 8.7	17.6 ± 4.5	31.1 ± 8.7	<0.001
Z-score (a.u.)	0.1 ± 0.6	0.0 ± 0.6	0.4 ± 0.6	0.003
Cognitive function, mean ± SD				
MoCA (score)	20.0 ± 6.3	19.2 ± 6.7	22.0 ± 4.7	0.004

SBP, systolic blood pressure; DBP, diastolic blood pressure; cfPWV, carotid-femoral pulse wave velocity; MoCA, Montreal Cognitive Assessment; a.u., arbitrary units.

The mediation analysis was performed to test whether physical fitness mediates the association between arterial stiffness (i.e. independent variable) and cognitive function (i.e. dependent variable). The mediation analysis was adjusted for age and gender. On the top of Figure 1 it is depicted the total effect [i.e. Equation (c)] between arterial stiffness and cognitive function (β = −0.329; p = 0.082). On left and right sides of the triangle, there are shown associations between arterial stiffness and physical fitness Z-score [Equation (a)] (β = −0.078; p < 0.001) and between physical fitness Z-score and cognitive function [Equation (b)] (β = 4.871; p < 0.001), respectively. Finally, the top of the triangle [Equation (c′)] reveals the direct effect of arterial stiffness on cognitive function (β = 0.053; p = 0.772), including the physical fitness Z-score in the model. The indirect effect of physical fitness Z-score was statistically significant (β = −0.382; 95% CI −0.670 to −0.138), confirming its mediation role between arterial stiffness and cognitive function.

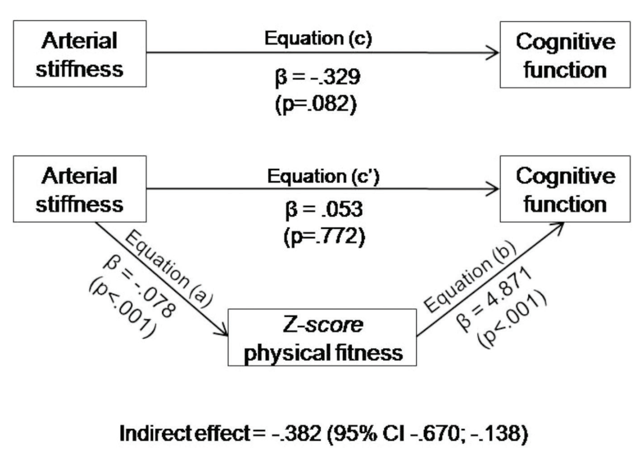

Figure 1 Physical fitness mediation model of the relationship between arterial stiffness and cognitive function, adjusted by sex and age.

4. DISCUSSION

The present study showed that physical fitness, independently of gender and age, is a mediator on the relationship between arterial stiffness and cognitive function in seniors.

An increased arterial stiffness results in augmented blood pressure and pulsatility to peripheral vessels and end organs [5]. The brain is sensitive to cardiovascular dynamics and consequently to an augmented arterial stiffness [4,5,22]. Repeated and prolonged exposure to a pulsatile flow affects cerebral microcirculation [22,23] which accelerates cognition impairment [24,25]. In fact, several studies found associations between arterial stiffness, cerebral vascular injury and cognitive decline [4,23,26]. Therefore, identifying factors to attenuate the damaged interface between heart and brain might be relevant in terms of public health.

Physical fitness is determined both by genetics and regular physical activity [8]. There are evidences showing that physical fitness is associated with better cognitive function [12,13] and arterial stiffness [11,27]. However, the evidence about the mediation role of physical fitness in the relationship between arterial stiffness and cognitive function is scarce.

High physical fitness, in particular cardiorespiratory fitness, is related with a better circulatory system function characterized by a better blood pressure, endothelial function [28], lipid profile [29], arterial compliance and autonomous nervous system activity [11]. Additionally, high physical fitness is also associated with a superior cerebrovascular function [11].

Despite most studies in the field of health and physical fitness are focused in cardiorespiratory fitness [11–13] it is important to highlight that ageing is a continuous process that affect the whole body. Indeed the neuromuscular system degeneration induces to important losses of strength, flexibility, balance and coordination that compromises senior's independency to perform daily life activities [30]. Indeed, in aging it is important to consider all health-related physical fitness components as crucial because they interact in order to sustained elders' independency for daily life activities. Therefore, results showed that the combination of health-related physical fitness components (i.e., *Z*-score) influenced the association between arterial stiffness and cognitive function. However, the isolated components (i.e. cardiorespiratory fitness, upper limb flexibility, lower and upper limb strength and dynamic agility and balance) were also mediators of the relationship between arterial stiffness and cognitive function (Data not shown.).

To the best of our knowledge, there is only one study including 102 elders with previous stroke (mean age 61 ± 9 years) that aimed to observe the mediation of physical fitness in the relationship between arterial stiffness and cognitive function [31], and the results were three. First, physical fitness was positively associated with cognitive function and inversely with arterial stiffness. Second, arterial stiffness was inversely associated with cognitive function. Third, the introduction of physical fitness into the regression model made the association between arterial stiffness and cognitive function no longer significant, leading the authors to conclude that physical fitness was a mediator of the association between increased arterial stiffness and decreased of cognition function.

Studies using the mediation analyses recommend as the best practice the use of indirect, direct and the total effect [21]. Although our results in terms of total effect were not significant, the indirect effect was. Mediation analysis does not require a significant association between dependent and independent variables (total effect) prior to the introduction of the mediator variable (indirect effect) [21,32]. The total effect is the result of the relationship between the independent variable and the dependent variable, without considering the mediator [21]. The indirect effect depicts the mediator influence on the relation between the dependent and independent variables and allows the classification of a specific variable as a mediator. Finally, recent mediation analyzes recommendations suggest that the inference should be based on the indirect effect value and on its statistical test that respects the non-normality of the sample distribution [21]. We choose the bootstrap confidence interval, which is the most recommended one [21].

4.1. Strengths and Limitations

The objective measurement of physical activity and the assessment of arterial stiffness via cfPWV give strength to this study. Conversely, limitations must be taken into consideration. Our study has a cross-sectional design, which does not allow examining cause-and-effect relationships between variables. In addition, sample size and non-random participants selection difficult the results transposition to other samples.

5. CONCLUSION

The present findings suggest that physical fitness, independently of gender and age, is a mediator on the relationship between arterial stiffness and cognitive function in seniors. A better physical fitness may contribute to the prevention of cognitive function decline caused by loss of arterial compliance.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTION

LB, JO and AN did study conceptualization and wrote (review and editing) the manuscript. AN, LB and DB did the data curation, formal analysis, and writing (original draft). JC and JO did the funding acquisition and project administration. LB and JC supervised the project.

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