Sex matters in the association between physical activity and fitness with cognition

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ABSTRACT

Purpose: The benefits from physical activity (PA) and cardiorespiratory fitness (CRF) on normal age-related cognitive decline might be sex-dependent. Our aim was to explore the relationship between different types of PA, CRF and cognition and to identify the mediating effects of CRF in the association between PA and cognition in women and men.

Methods: We recruited 115 healthy adults aged 50-70 years. We obtained demographic, cognitive and PA status data based on Projecte Moviment Protocol. We calculated cognitive domains by grouping z-sample scores. We obtained self-reported total energy expenditure during the last month and grouped it into sportive PA (S-PA) and non-sportive PA (NS-PA). CRF was estimated using the 1-mile Rockport Walk Test. We applied regression models and mediation analyses in a final sample of 104 individuals (65 women and 39 men).

Results: In the total sample, CRF was positively associated with Executive Function, Verbal Memory and Attention-Speed. S-PA was positively related to Executive Function and Attention-Speed while NS-PA was unrelated to cognitive domains. Greater amounts of S-PA were associated with Executive Function and Attention-Speed for both women and men. Higher CRF was associated with Executive Function, Memory, Language and Attention-Speed only in men. Mediation analyses showed that CRF was a significant mediator of the positive effects of S-PA on Executive Function and Attention-Speed in men but not in women.

Conclusions: Both women and men show cognitive benefits from greater S-PA, but not from NS-PA. However, there were sex differences in the mediating effects of CRF in this relationship showing that CRF was mediating these benefits only in men.

Keywords: cognitive performance, sex-differences, exercise, cardiorespiratory fitness, healthy adults.

INTRODUCTION

Yes, your lifestyle may be predictive of future cognitive decline. Aging is related to normal late-life cognitive decline even for those who do not experience dementia or other neurodegenerative pathologies (1). Executive function, processing speed, memory and psychomotor ability deteriorate over the lifespan and may alter daily function and well-being (2). However, an active lifestyle may benefit cognitive health (3) and improve or maintain specific cognitive domains when applied as interventions (4).

Physical activity (PA), defined as daily movements involving skeletal muscles that result in energy expenditure (5), is an essential factor of an active lifestyle for brain health (3). Higher levels of PA protect against cognitive decline and reduce the risk for dementia (6). In cross-sectional studies, PA is significantly related to better processing speed and executive function (7). There are mixed results about the relationship between PA and episodic verbal memory (7,8). PA measures (e.g. questionnaires and actimeters) differ across studies and may explain heterogeneous results. One remaining question is whether any type of PA is sufficient for improving cognition or whether exercise, defined as a structured and repetitive subtype of PA that aims to improve physical fitness (5), through moderate to vigorous intensity levels, is necessary (9). Reviews of exercise intervention studies report that exercise has significant but modest positive effects on cognitive performance, especially on executive function (10-12), when interventions consist of aerobic exercise programs (10,11) or last at least 52 hours (13). However, there is a lack of literature clearly reporting differences in the relationship between exercise (sportive PA), other types of daily PA (non-sportive PA) and cognition in cross-sectional and longitudinal studies.

Cardiorespiratory fitness (CRF) is a widely used measure to describe the relationship between cognition and cardiovascular health related to exercise. Maximal aerobic capacity (VO_2max)

is the gold standard measure to assess CRF. In cross-sectional studies, higher CRF, directly estimated through progressive exercise tests, has been related to better scores in global cognitive function, executive function (14,15), attention (14) and verbal (15) and spatial memory (16). Interventional studies showed that participants in aerobic exercise programs significantly increased CRF and improved cognitive functions (17). However, evidence is still insufficient to prove that those CRF changes are significantly related to cognitive improvements (18). Relevant reviews in this field (9,12,18) highlight methodological, PA variables and individual-related factors to explain these discrepancies. One major issue is to explore the mediating effect of CRF in the relationship between PA and cognition in cross-sectional studies to better understand its role as a mechanism of cognitive benefits related to PA.

Current trends focus on understanding individual difference variables that explain variation in the effects of PA in order to improve personalized interventions for enhancing cognitive function. Meta-analytic studies examining the effects of aerobic training interventions in healthy older adults reported greater effect sizes on executive function in the whole group when samples had >50% of females (10,11). Sex differences in randomized controlled trials (RCTs) have not been studied with healthy populations yet. RCTs including participants with mild cognitive impairment and vascular cognitive impairment found greater improvements in executive function in women (19,20). Sex differences related to PA and cognition have been scarcely assessed in cross-sectional and longitudinal studies. Hogervorst and colleagues (21) reported an association between greater amounts of PA and a greater reduction in the risk for dementia in women. Similarly, Barha and colleagues (22) reported that greater amounts of PA over 10-years was associated with less decline in executive functions and processing speed in women. Other discrepant results showed that self-reported PA was related to better performance in Mini-Mental State Examination (MMSE) and executive functions in men but not in women (23). Sex has become a relevant matter since it is considered an important moderator of the effects of PA on cognition (11,24). Current reviews underline the fact that studies should address potential sex differences and describe potential physiological mechanisms such as sex steroids hormones and differences in the musculoskeletal and cardiorespiratory adaptations after exercise (24). Given the fact that women and men show different patterns of CRF across the lifespan (25), the mediating effects of CRF in the relationship between PA and cognition should be assessed in women and men separately.

In this proof-of-concept study we addressed previously described gaps that exist in the literature assessing sex differences in relation to PA, CRF, and cognition. First, our aim was to explore the relationship between different types of PA, CRF and cognition in the total sample, then assess the moderating effect of sex in these relationships by stratifying the results to examine effects in women and men. Second, we aim to identify the mediating effects of CRF in the association between PA and cognition in women and men. To our knowledge, there is not a previous literature describing the role of sex in the relationship between PA and cognitive performance including CRF as a mediator.

METHODS

Study Design

This is a cross-sectional study based on Projecte Moviment (26) which is a RCT that aims to study the effect of aerobic exercise, cognitive training and the combination on cognition. For this study, we used the baseline assessments belonging to the Projecte Moviment sample and 20 additional participants with a higher physical activity profile. All participants were recruited and selected following the same procedures described in the cited protocol (26) and during the same period of time. The University of Barcelona led this research and the corresponding ethics committee following the Declaration of Helsinki approved it.

Participants

One hundred and fifteen community-dwelling healthy adults were recruited. Participants were eligible for this study if they were 50-70 years old, were not cognitively impaired as defined by the MMSE≥24 (27) and the Montreal Cognitive Assessment 5-min (MoCA-5min≥6) (28), had competency in Catalan or Spanish and had adequate sensory and motor skills. Participants from the Projecte Moviment trial were eligible if they did not perform structured sportive PA more than 2 hours/week over the last 6 months, whereas additional participants had to do at least 5 hours/week of moderate PA or 2.5 hours/week of intensive PA. We excluded individuals who had a neurological diagnosis, psychiatric disease and Geriatric Depression Scale>9 (29), a history of drug abuse and alcoholism or consumed psychopharmacological drugs (see Table, SDC 1, which contains extended details).

Assessment

Participants meeting criteria went through a multimodal assessment described elsewhere (26). We selected only the demographic data and baseline cognitive and physical status outcomes needed to address our specific aims. We instructed participants not to exercise before the appointment and cognitive tests were administered before the CRF test to control for the effect of acute exercise.

Demographic data and Cognitive assessment

We registered age, sex and years of education of all participants. As cardiovascular health variables, we obtained the body mass index (BMI) -using weight and height- and collected data about diagnoses of hypertension and diabetes.

We assessed cognitive function using an extensive neuropsychological battery which included: Stroop Test (30), Wechsler Adult Intelligence Scale III (WAIS-III; subtests: forward and backward digit span, vocabulary, digit symbol coding, symbol search) (31) Trail Making Test A & B (TMT A & B) (32), Verbal Fluency Test (33), Rey-Osterrieth Complex Figure (ROCF) (34), Rey Auditory Verbal Learning Test (RAVLT) (35) and Boston Naming Test (BNT) (36). This comprehensive cognitive assessment was also used to clinically confirm the lack of MCI or dementia.

Self-reported PA

We applied the reduced Minnesota Leisure Time Physical Activity Questionnaire (37) to obtain self-reported PA. This questionnaire asked participants the number of hours performed during the last month in the following categories: sportive walking, sports, gardening, climbing stairs, shopping walking and cleaning house. Moreover, for the sports category, participants had to specify how many and which sports were they performing and for the climbing stairs, participants had to estimate the amount of stairs climbed per day.

Cardiorespiratory fitness

We assessed CRF using the Rockport 1-Mile Walking Test which is useful for accurately estimating VO_2 max. in healthy older adults (38). We instructed participants to walk one mile on a treadmill (Technogym®, Italy) adjusting their speed in order to be as fast as possible without running. Maximal aerobic capacity (VO_2 max) was estimated with the standard equation developed by Kline and colleagues (39) using the following variables: weight, age, sex, time to complete the mile and heart rate at the end of the test.

Statistical analyses

The data were analyzed using IBM SPSS Statistics for Windows, Version 24.0. Demographics and physical status variables were analyzed in the total sample and by sex. We calculated z-sample scores for all neuropsychological tests and grouped them following a theoretical-driven approach based on the classification of tests in previous literature (40,41). First, we calculated nine domains: Inhibition (interference-Stroop Test), Working Memory (backward-WAIS-III), Flexibility (TMT B-A), Fluency (letter and category fluency), Visuospatial Function (copy accuracy-ROCF), Verbal Memory (total learning and recall-II RAVLT), Visual Memory (memory accuracy-ROCF), Language (BNT-15), Attention (forward span, digit symbol coding and symbol search WAIS-III) and Speed (TMT-A, copy time-ROCF). Then, we designed five general domains: Executive Function, Visuospatial Function, Memory, Language and Attention-Speed.

We transformed hours per month expended in each category from the Minnesota Questionnaire into units of the metabolic equivalent tasks (METs). We calculated Total PA by summing all METs spent in different activities. Based on the previous definition of exercise (5), we then grouped activities into the following categories: Sportive PA (S-PA) –sportive walking and sports activities- and Non-Sportive PA (NS-PA) -gardening, climbing stairs, shopping walking and cleaning house- and calculated METs values separately for both categories.

Linear regression models were performed to examine the association between CRF and different types of PA with cognitive outcomes in the total sample. Age, years of education and sex were included as covariates. We analyzed the role of sex in the relationship between physical and cognitive outcomes regressing physical status outcomes on cognitive performance for women and men, accounting for age and years of education.

Finally, we applied mediation analyses using the PROCESS Macro (42) in women and men (Figure 1). Path C tested if the independent variable (PA) was associated with the dependent variable (cognitive composites) controlling for age and years of education. Path A was a regression between the independent variable (PA) and the mediator (CRF) accounting for the same covariates. Path B determines if mediator (CRF) changes predict changes in the dependent variable (cognitive composites) accounting for the same covariates. These analyses allowed us to obtain the estimated direct (Path C') and the indirect effect (Path AB). Path C' reports the association between the independent variable (PA) and cognitive outcomes when the mediator (CRF) and covariates are included in the model. Path AB represents the association with the mediator (CRF) in the model. These analyses were computed with bias-corrected bootstrap 95% confidence intervals (CIs) based on 5,000 bootstrap samples. Significance of mediation was indicated if the CIs in Path AB did not overlap with 0 (42).

RESULTS

Participants

One hundred fifteen adults were recruited and assessed. The CRF measure could not be estimated for eleven participants, so all analyses were conducted on 104 participants (age=57.44 ± 5.36; 63% female; years of education=13.35 ± 5.29; MMSE=28.22 ± 1.45; BMI=27.52 ± 4.91). The 65 women and 39 men included in the sample showed no significant differences in the demographic data, except in years of educations that is used as a covariate (see Table 1). There was a similar and significant correlation between S-PA and CRF in women ($r=.551$, $p<.001$) and men ($r=.631$, $p<.001$) despite sex differences in S-PA and CRF (see Table

1). There were no significant differences in the demographic variables between participants of Projecte Moviment and the 20 additional participants (see Tables, SDC 2, extended details).

Association between PA, CRF and cognition

Linear regression models examining the association between CRF and different types of PA with cognitive domains in the total sample are in Table 2. Higher CRF was related with better Executive Function, specifically Working Memory, Flexibility and Fluency subdomains; Memory, especially Verbal Memory; and Attention-Speed, both subdomains: Attention and Speed. Greater S-PA was related to better Executive Function, specifically to Working Memory and Fluency; and to Attention-Speed, including Attention and Speed. However, NS-PA was not associated with any cognitive measure.

Sex differences in the relationship between PA, CRF and cognition

Table 3 provides the linear regression models stratified by sex. For women**,** CRF was not significantly associated with cognitive performance in any domain. For men, CRF was positively related to Executive Function, including Inhibition, Working Memory and Fluency; Memory, notably Verbal Memory; Language and Attention-Speed, including both subdomains: Attention and Speed. S-PA was significantly associated with Executive Function especially with Fluency, and Attention-Speed in women and men respectively (see Figure 2). To further confirm the significance of the sex moderation we performed moderation analyses (see Table, SDC 3).

Sex differences in the mediation effects of CRF

We applied mediation analyses for each cognitive outcome using CRF as a mediator for women and men separately (Table 4). We used S-PA as an independent variable given its similar significant association with cognition in women and men.

Women. Path C was equivalent to previous linear regression models for women in Table 3. Path A showed a significant relationship between S-PA and CRF (β=.47, $p<.001$) accounting for age and years of education. Path C' and AB, indicated that CRF did not mediate the association between S-PA and cognitive outcomes in women.

Men. Path C was equivalent to previous linear regression models for men in Table 3. Path A showed a significant relationship between S-PA and CRF (β=.64, $p<.001$.) accounting for age and years of education. Path C' and AB showed maximum evidence for mediation of CRF in Executive function especially in Fluency; and Attention-Speed, with Attention as the significant subdomain.

DISCUSSION

In this paper, we first aimed to explore the relationship between different types of PA, CRF and cognition in the total sample. CRF emerged as a key factor of cognitive health as results showed that higher estimated CRF was significantly associated with better performance on Executive Function, Verbal Memory and Attention-Speed in the whole sample. Those results support previous literature stating CRF is related to better performance in executive functions, attention and memory (14,15). We found interesting results when we grouped PA into S-PA and NS-PA suggesting that only the sportive subtype was related to cognitive performance. S-PA had a positive relationship with Executive Function and Attention-Speed while NS-PA had not. Our results clearly relate cognitive benefits specifically to S-PA and not to NS-PA adding support to the fact that PA should not be mistaken for exercise (43). This fact highlights the importance of the "sportive" component of the PA when prescribing PA to people. This "sportive" component might be related to differences in PA parameters such as frequency, dose and intensity between S-PA and NS-PA as well as other psychosocial parameters such as the social interaction and well-being enhanced when exercising (44,45).

In our study, results suggested that sex mattered. Sex moderated the association between CRF and cognition, but not for S-PA. S-PA was significantly associated with Executive Function and Attention-Speed for both women and men. Interestingly, CRF was not significantly related to cognitive performance in women but it was positively associated with Executive Function, Verbal Memory, Language and Attention-Speed in men. Thus, our results not only add support to the cognitive benefits related to regular exercise in both women and men but also opens the debate of the potential sex-dependent role of CRF in these benefits. CRF is a parameter highly related to exercise but also influenced by other variables such as sex (25,46) which might lead to differences in the exercise-related benefits.

Sex mattered again when analyzing the mediating effects of CRF in the association between PA and cognition in women and men. We introduced S-PA in the model given the fact that our previous results suggested that benefits are related specifically to exercise. In men, CRF was a significant mediator of the positive relationship between S-PA and Executive Functions and Attention-Speed but CRF was not a significant mediator in women. These results add support to sex-dependent role of CRF in the exercise-related benefits in cognition. Sex differences in CRF across the lifespan have already been described reporting lower levels in females and related to physiological, social and behavioral parameters (25). On one side, they have been related to structural and functional differences in the respiratory, musculoskeletal and cardiovascular system. Thus, women and men differ in the physiological responses of these systems after exercise (24). Exercise benefits cardiovascular health more in men than in women: studies report lower blood pressure, increased blood flow and less endothelial dysfunction in males (24,47). On the other side, and in accordance with our results, previously published literature reported that men and women differ in the amount of exercise performed, being men more physically active (25). However, we found a similar and significant correlation between S-PA and CRF in women and men. Therefore, our results suggest sex differences in the mediating effects of CRF in the relationship between cognition and exercise in healthy adults which might be related to physiological and behavioral causes.

However, it remains an interesting question: if not CRF what is mediating the exercise-related cognitive benefits in women? This requires an answer that goes beyond the scope of this paper. Previous literature suggest that regular exercise is known to origin a cascade of changes at a molecular, cellular, brain and psychological level which might be different for women and men. For example, increases in sex steroids after acute and chronic exercise may positively impact BDNF levels, neuroplasticity and cognition in women and men (11). However, there are well-known differences in the sex steroids hormones across the lifespan between women and men that might influence cognition (48). Therefore, sex-differences in physiological correlates mediating the relationship between PA and cognition, such as steroid hormones, must be addressed.

Strengths and limitations

We included a comprehensive neuropsychological assessment allowing us to determine the extent of these sex differences, an objective estimation of CRF and measurements of self-reported PA commonly used in previous studies which we categorize into different subtypes in order to observe discrepancies as was suggested in a previous review (9,11). However, although Rockport 1-Mile Walking test is a less invasive and valid technique to administer to elderly athletes and non-athletes (38), it is not a direct physiological measurement of VO2max. Further studies should examine those preliminary results in samples with different PA and CRF profiles to assess if this could be a potential confound. It could be interesting to explore those results in different age groups, using a direct measure of VO2max and controlling for the history of PA, which may influence current physical and cognitive health.

Conclusions and future recommendations

To our knowledge, our study is one of the first to relate cognitive benefits specifically to the sportive component of PA and to report sex differences in the mediating effects of CRF in the relationship between S-PA and cognitive performance. We hypothesize that the mediating effects of CRF might be different in women and men given sex-differences in the physiological correlates that shape CRF and we suggest other potentially involved mechanisms.

Our results highlight the fact that sex must be included as a moderator in cross-sectional and RCTs of this field studying the effect of an intervention and its relationship with change in PA activity outcomes. These results add support to the importance of individual factors to understand the effects of exercise on cognitive health and its underlying physiological mechanisms as well as to improve the design of personalized interventions. Determining the causes of the observed difference between women and men goes beyond the scope of this paper but will be included in our future aims.

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Author Contributions. ACS and FRC were involved in the study concept and design, acquisition, analyses and interpretation of data as well as in elaboration of the manuscript. NLV and AB collaborated in the acquisition of the data. NLV, PT, GP, PM, AB, RDA, LB, KE critically reviewed the content of the article. MM conceptualized the study, contributed to the study design and the implementation as Principal Investigator and supervised all procedures and the elaboration of the manuscript.

Conflict of Interest. None. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by ACSM.

Patient Consent. Obtained.

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Figure legends

Figure 1. Mediation analyses template.

Figure 2. Circos plot of partial correlations between physical status outcomes and cognitive domains adjusting for age and years of education for men and women. Ribbon width indicates percentage of explained variance. The color of the ribbon corresponds to the color of the original segment for $p<.05$ correlations. Grey ribbons refer to non-significant correlations. (See Figure, SDC 4, which contains values for partial correlations) (49).

Note: Att: attention, Att-Sp: attention-speed; CRF: cardiorespiratory fitness; EF: executive function; Fl: fluency; Flex: flexibility; Inh: inhibition; LNG: language; MMR: memory; NS-PA: non-sportive physical activity; Sp: speed; S-PA: sportive physical activity; Vb-M: verbal memory; VF: visuospatial function; Vs-M: visual memory; WM: working memory.

Table 1. Demographic and physical status variables

	Women	**Men**	
Demographic variables	Mean (SD)	Mean (SD)	t-Test / χ^2 (*p* Value)
n	65	39	-
Age (years)	56.75 (4.96)	58.59 (5.86)	1.64 (.106)
Education (years)	12.46 (4.97)	14.82 (5.55)	2.18 (.032)
MMSE (/30)	28.15 (1.41)	28.33 (1.53)	.60 (.552)
BMI	26.99 (4.53)	28.40 (5.44)	-1.43 (.157)
Hypertension (n)	12	10	3.46 (.063)
Diabetes (n)	7	4	3.59 (.058)
Physical status variables	Mean (SD) [Min – Max]	Mean (SD) [Min – Max]	t-Test (*p* Value)
Total-PA	11551.23 (7746.10) [1647-36468]	12184.51 (11898.78) [600-39454]	-.30 (.768)
S-PA	2055.35 (4395.04) [0 - 16512]	6011.35 (9939.24) [0 - 36952]	-2.35 (.023)
NS-PA	9495.88 (6438.50) [1260- 29232]	6173.16 (6780.93) [600 - 39120]	2.50 (.014)
CRF	25.07 (12.31) [0.07 - 49.68]	33.86 (12.92) [3.09- 58.64]	-3.46 (.001)

Note: MMSE= Mini-Mental State Examination; Total-PA = Total Physical Activity; S-PA = Sportive Physical Activity; NS-PA = Non-Sportive PA; CRF = Cardiorespiratory fitness

Table 2. Association between physical status outcomes and cognition; lineal regression models for total sample.

Cognitive Domains	**CRF** R^2; β (*p* Value)	**Total-PA** R^2; β (*p* Value)	**S-PA** R^2; β (*p* Value)	**NS-PA** R^2; β (*p* Value)
EXECUTIVE FUNCTION	0.11; 0.29 (.012)*	0.10; 0.24 (.014)*	0.15; 0.34 (.001)**	0.05; -0.00 (.990)
Inhibition	0.03; 0.08 (.490)	0.04; 0.12 (.237)	0.04; 0.12 (.256)	0.03; 0.05 (.614)
Working Memory	0.14; 0.26 (.017)*	0.11; 0.15 (.119)	0.16; 0.28 (.004)**	0.09; -0.08 (.426)
Flexibility	0.28; 0.21 (.038)*	0.25; 0.03 (.716)	0.26; 0.14 (.121)	0.26; -0.10 (.256)
Fluency	0.24; 0.37 (<.001)***	0.19; 0.24 (.012)*	0.24; 0.34 (<.001)***	0.13; -0.01 (.890)
VISUOSPATIAL FUNCTION	0.29; 0.13 (.178)	0.27; 0.04 (.642)	0.28; 0.10 (.260)	0.27; -0.05 (.596)
MEMORY	0.31; 0.33 (.001)**	0.25; 0.16 (.079)	0.25; 0.16 (.089)	0.23; 0.07 (.472)
Verbal Memory	0.27; 0.36 (<.001)***	0.21; 0.18 (.050)*	0.20; 0.15 (.108)	0.18; 0.11 (.269)
Visual Memory	0.29; 0.11 (.255)	0.28; 0.04 (.655)	0.29; 0.09 (.320)	0.28; -0.04 (.676)
LANGUAGE	0.28; 0.10 (.316)	0.29; 0.15 (.091)	0.30; 0.17 (.061)	0.27; 0.04 (.650)
ATTENTION-SPEED	0.43; 0.26 (.004)**	0.40; 0.15 (.056)	0.43; 0.24 (.004)**	0.38; -0.03 (.765)
Attention	0.39; 0.24 (.012)*	0.36; 0.13 (.131)	0.39; 0.23 (.006)**	0.35; -0.06 (.465)
Speed	0.35; 0.26 (.006)**	0.33; 0.17 (.040)*	0.34; 0.20 (.019)*	0.30; 0.04 (.640)

Note: CRF = Cardiorespiratory fitness; Total-PA = Total Physical Activity; S-PA = Sportive Physical Activity; NS-PA = Non Sportive PA

Covariates: age, years of education and sex.

* p < .05; ** p <.01; *** p<.001;

Table 3. Association between physical status outcomes and cognition; linear regression models for women and men.

Cognitive Domains	**WOMEN**		**MEN**	
	CRF R^2, β (*p* Value)	**S-PA** R^2, β (*p* Value)	**CRF** R^2, β (*p* Value)	**S-PA** R^2, β (*p* Value)
EXECUTIVE FUNCTION	0.01; 0.03 (.848)	0.10; 0.31 (.016)*	0.41; 0.63 (<.001)***	0.23; 0.40 (.014)*
Inhibition	0.07; -0.13 (.369)	0.11; 0.22 (.087)	0.14; 0.39 (.022)*	0.01; 0.08 (.638)
Working Memory	0.04; 0.09 (.532)	0.06; 0.17 (.181)	0.22; 0.46 (.005)**	0.18; 0.39 (.015)*
Flexibility	0.32; 0.15 (.216)	0.33; 0.19 (.076)	0.21; 0.27 (.110)	0.16; 0.11 (.477)
Fluency	0.13; 0.15 (.273)	0.20; 0.31 (.011)*	0.51; 0.62 (<.001)***	0.32; 0.39 (.010)*
VISUOSPATIAL FUNCTION	0.31; 0.04 (.775)	0.32; 0.11 (.331)	0.28; 0.22 (.146)	0.24; 0.08 (.575)
MEMORY	0.25; 0.20 (.115)	0.22; 0.04 (.708)	0.41; 0.44 (.003)**	0.29; 0.22 (.135)
Verbal Memory	0.16; 0.25 (.063)	0.11; 0.03 (.790)	0.37; 0.47 (.002)**	0.22; 0.23 (.142)
Visual Memory	0.25; 0.04 (.773)	0.25; 0.04 (.715)	0.30; 0.17 (.253)	0.29; 0.12 (.417)
LANGUAGE	0.18; -0.05 (.729)	0.20; 0.15 (.202)	0.43; 0.34 (.016)*	0.38; 0.23 (.099)
ATTENTION-SPEED	0.36; 0.12 (.301)	0.40; 0.22 (.034)*	0.52; 0.47 (.001)**	0.40; 0.29 (.036)*
Attention	0.37; 0.09 (.462)	0.40; 0.21 (.042)*	0.40; 0.43 (.005)**	0.31; 0.27 (.067)
Speed	0.25; 0.15 (.233)	0.27; 0.20 (.077)	0.46; 0.44 (.002)**	0.35; 0.26 (.069)

Note: CRF = Cardiorespiratory fitness; S-PA = Sportive Physical Activity

Covariates: age and years of education

* p <.05; ** p <.01;*** p<.001

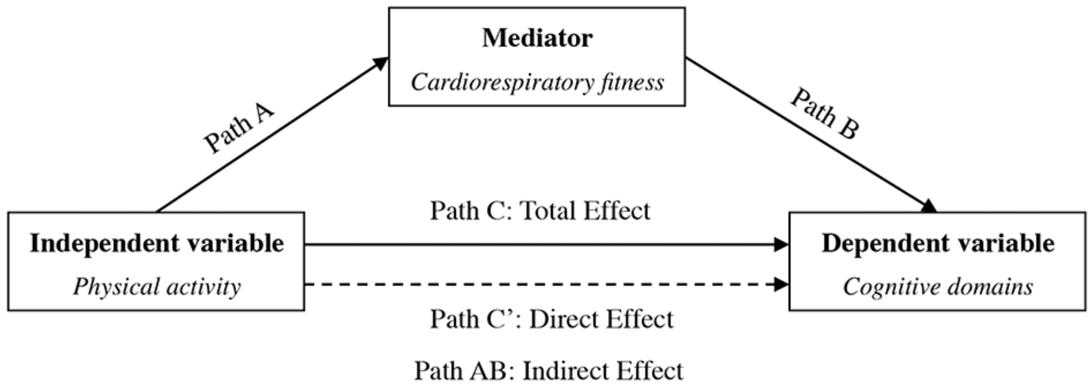
Table 4. Mediation analyses.

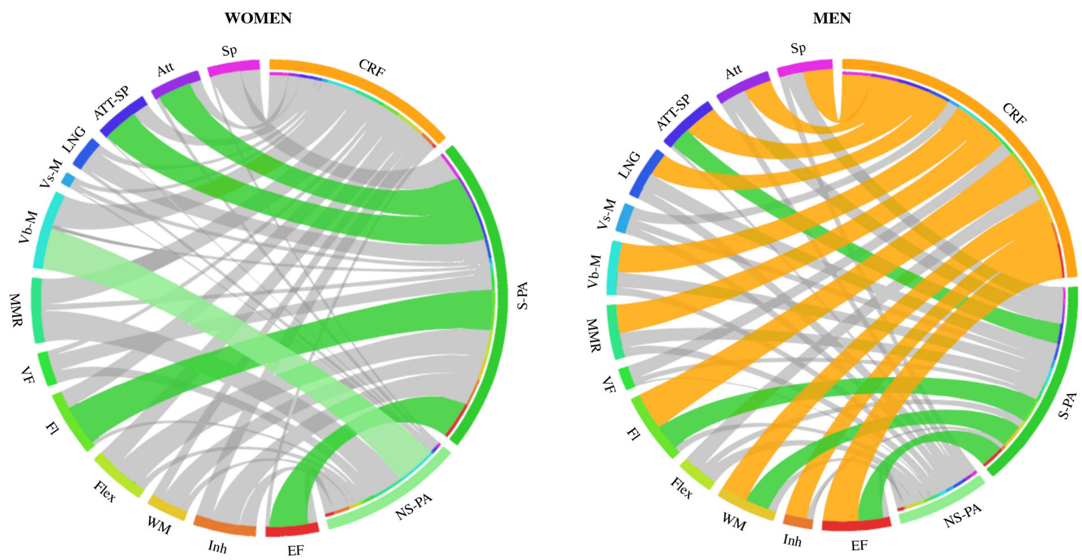
	Cognitive Domains	Path C' β_2 (SE), *p* Value [95%CI]	Path AB β_{AB} (SE), [95%CI]
WOMEN	EXECUTIVE FUCNTION	0.41 (0.00), .007 [0.00, 0.00]	-.010 (0.08) [-0.28, 0.06]
	Inhibition	0.38 (0.00), .010 [0.00, 0.00]	-.016 (0.06) [-0.30, -0.05]
	Working Memory	0.18 (0.00), .239 [0.00, 0.00]	-0.01 (0.09) [-0.18, 0.16]
	Flexibility	0.17 (0.00), .188 [0.00, 0.00]	0.03 (0.07) [-0.11, 0.17]
	Fluency	0.33 (0.00), .021 [0.00, 0.00]	-0.02 (0.08) [-0.18, 0.12]
	VISUOSPATIAL FUNCTION	0.12 (0.00), .339 [0.00, 0.00]	-0.02 (0.08) [-0.17, 0.16]
	MEMORY	-0.07 (0.00), .606 [-0.00, 0.00]	0.11 (0.07) [-0.01, 0.25]
	Verbal Memory	-0.12 (0.00), .412 [-0.00, 0.00]	0.15 (0.07) [0.01, 0.30]
	Visual Memory	0.03 (0.00), .802 [-0.00, 0.00]	0.01 (0.08) [-0.16, 0.17]
	LANGUAGE	0.24 (0.00), .089 [0.00, 0.00]	-0.09 (0.07) [-0.24, 0.04]
	ATTENTION-SPEED	0.23 (0.00), .066 [0.00, 0.00]	-0.00 (0.07) [-0.14, 0.12]
	Attention	0.23 (0.00), .056 [0.00, 0.00]	-0.02 (0.07) [-0.16, 0.11]
	Speed	0.18 (0.00),.181 [0.00, 0.00]	0.02 (0.07) [-0.11, 0.15]
MEN	EXECUTIVE FUNCTION	0.01 (0.00), .951 [0.00, 0.00]	0.39 (0.15) [0.09, 0.69]*
	Inhibition	-0.31 (0.00), .147 [-0.00, 0.00]	0.39 (0.11) [0.21, 0.63]
	Working Memory	0.17 (0.00), .392 [0.00, 0.00]	0.22 (0.16) [-0.08, 0.55]
	Flexibility	-0.10 (0.00), .632 [-0.00, 0.00]	0.21 (0.14) [-0.05, 0.49]
	Fluency	-0.01 (0.00), .974 [0.00, 0.00]	0.39 (0.13) [0.14, 0.64]*
	VISUOSPATIAL FUNCTION	-0.11 (0.00), .587 [0.00, 0.00]	0.19 (0.16) [-0.15, 0.47]
	MEMORY	-0.10 (0.00), .565 [0.00, 0.00]	0.33 (0.16) [-0.04, 0.61]
	Verbal Memory	-0.13 (.00), .484 [-0.00, 0.00]	0.36 (0.16) [0.00, 0.65]
	Visual Memory	0.01 (0.00), .945 [0.00, 0.00]	0.10 (0.13) [-0.19, 0.33]
	LANGUAGE	0.02 (0.00), .914 [0.00, 0.00]	0.21 (0.15) [-0.15, 0.46]
	ATTENTION-SPEED	-0.02 (0.00), .915 [0.00, 0.00]	0.31 (0.12) [0.09, 0.57]*
	Attention	-0.00 (0.00), .998 [0.00, 0.00]	0.27 (0.13) [0.05, 0.56]*
	Speed	0.04 (0.00), .799 [0.00, 0.00]	0.30 (0.15) [-0.00, 0.59]

Notes: * significant values (p<.05 in path C; *interval not containing zero in path AB)

Path C' [Direct effects]: Cognitive Domain = β_2S-PA (β_3CRF) + (covariates) + $\beta_{0;}$

Path AB [Indirect effects]: Path C – Path C'


Mediator
Cardiorespiratory fitness
Path A
Path B
Path C: Total Effect
Independent variable
Physical activity
Dependent variable
Cognitive domains
Path C': Direct Effect
Path AB: Indirect Effect


WOMEN
MEN
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