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Mean arterial pressure, fitness, and executive function in middle age and older adults

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ABSTRACT

Previous literature suggests that higher fitness is related to better executive function in older adulthood, but the mechanisms underlying this association are poorly understood. While many studies have focused on these associations in older adulthood, recent evidence suggests the importance of cardiorespiratory fitness (CRF) and long-term blood pressure control on cognitive functioning. The purpose of the current study was to examine whether mean arterial pressure (MAP) mediated the association between CRF and executive function in middle age and older adults. Participants were adults (age 40+) without any self-reported psychiatric and neurological disorders or cognitive impairment from the Nathan Kline Institute Rockland Sample (N = 224, M age = 56). CRF was defined by VO_{2max} estimated via a bike test, neuropsychological testing was used to examine executive functioning, and MAP was calculated from systolic and diastolic blood pressure recordings. Mediation models were analyzed controlling for age, sex, and education. Results indicated that higher CRF was associated with better inhibition (B = -0.0048, t = -2.16, p = 0.03) and there was a significant indirect effect of greater CRF on better inhibition through lower MAP (B = -0.0011; CI [-0.0026, -0.0002]). There were additional significant indirect effects of greater CRF and better fluency (B = 0.0028; CI [.0009, 0.0053]) and planning (B = 0.0037; CI [.0014, 0.0074]) through lower MAP. This suggests that MAP may be an underlaying physiological mechanism by which CRF influences executive function in mid- and older adulthood.

Introduction

Physical activity and associated gains in fitness have been shown to be neuroprotective for older adults, with evidence suggesting preserved brain structure [7,8], function [53], and better cognitive functioning [38]. Many recent meta-analyses suggest that exercise interventions and subsequent gains in fitness may have a selective effect on cognition in older adulthood, with the greatest impact on executive functioning [10, 28,47]. Executive functioning is an important set of higher-order cognitive skills that include inhibition, planning, fluency, and switching between tasks [14]. Not only are these skills especially important for maintaining independence in older adulthood [22], but some evidence suggests that changes in executive function may be occurring earlier in middle age [20] and may be predictive of future cognitive decline [29]. Therefore, there is a need to examine how fitness may be related to executive function across a younger adult sample.

Cardiorespiratory fitness (CRF) is a measure of the ability of the circulatory and respiratory systems to deliver oxygen, and the peak rate at which oxygen can be consumed, during sustained physical activity at a maximal effort [45]. As a consequence of genetic makeup, overall vascular health, and engagement in vigorous or sustained physical activity, CRF has emerged as an important measure of physical health [25, 43]. Higher CRF has been shown to be related to greater brain volume [41], particularly in gray matter regions like the prefrontal cortex [17]. Higher CRF has also been associated with preserved white matter integrity [24], and functional connectivity [6,52], as well as better cognitive functioning [51] in older adults. However, the mechanisms underlying these positive effects are not fully understood. Several studies suggest that increased cerebral blood flow may be the mechanism by which greater CRF is associated with better cognitive outcomes in aging [1,9]. Cerebral perfusion can be impacted by many factors, notably blood pressure. Moreover, exercise and greater CRF are among the most potent non-pharmacological interventions to reduce hypertension and maintain healthy blood pressure in across the adult lifespan

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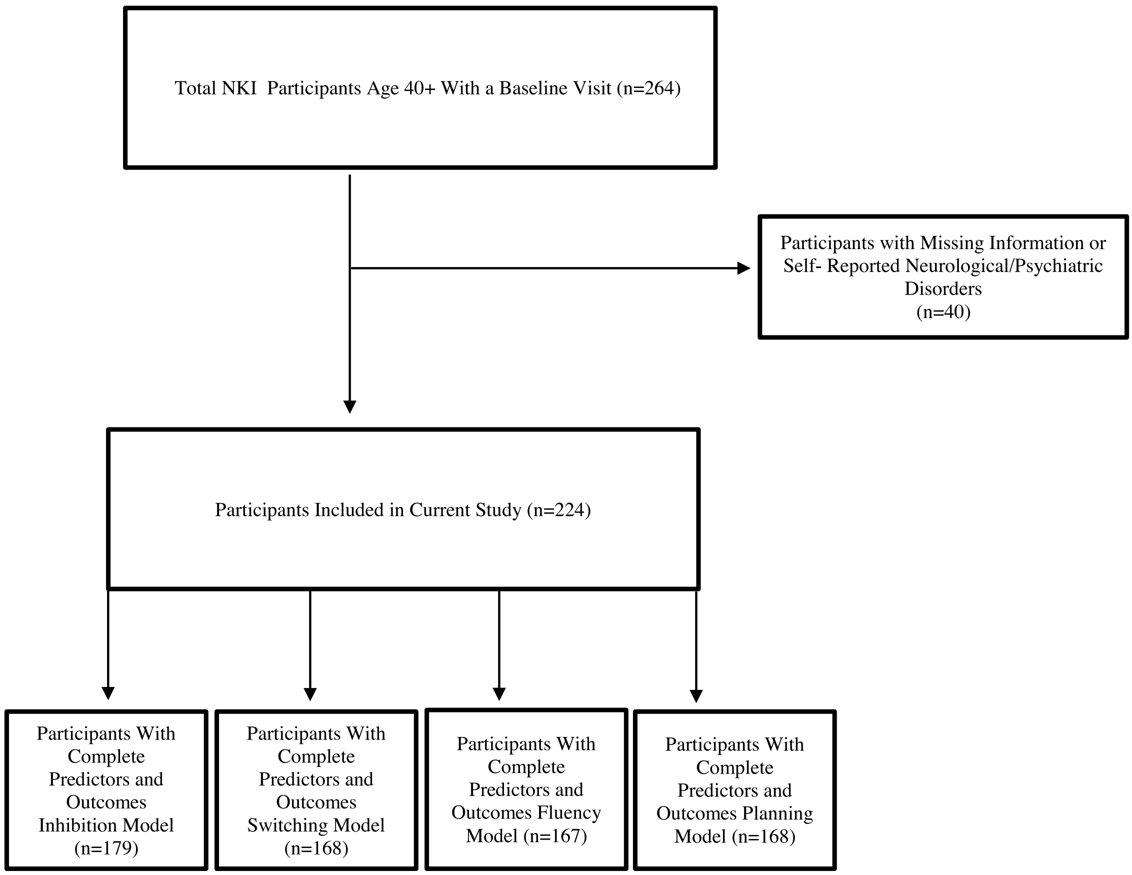

Fig. 1. Study flowchart.

[2,12]. Mean arterial pressure (MAP) reflects both systolic and diastolic blood pressure during each cardiac cycle and provides an estimate of perfusion [36]. Even subclinical cerebral hemodynamics in older adulthood have been shown to impact brain structure and function [33]. In particular, frontal-subcortical networks appear to be particularly impacted by vascular dysfunction [11], and dysfunction in cerebral autoregulation can negatively impact executive function [50]. Thus, executive dysfunction often occurs as a result of vascular damage [39]. A recent systematic review examined the components of executive function most impacted by systemic arterial hypertension and found that inhibition and shifting were most impacted [34]. While this is well-documented in older adulthood, less evidence exists examining this relationship in middle age and younger older adults. Some evidence suggests that vascular health during middle adulthood is a critical time for intervention [32]. Therefore, it is important to understand factors that might mitigate vascular dysfunction on brain health and cognition.

The purpose of the current study was to examine whether MAP mediated the associations between CRF and several aspects of executive function (i.e., inhibition, fluency, planning, switching) in a large sample of participants ranging from middle age to older adulthood. This study contributes to the current literature by utilizing a sample with greater diversity in age than is typically examined and by examining the mechanisms by which CRF may be neuroprotective. We hypothesize that greater CRF will be associated with better executive function in all domains. We also hypothesize that MAP will mediate the association between CRF and executive function, particularly in inhibition and switching models [34].

Table 1
Descriptive statistics.

Variable	% or M (SD)
Demographics	
Age	56.75 (9.05)
Sex (% female)	71.9%
Race/Ethnicity (% White)	84.4%
Years of Education	16.20 (4.16)
Mean Arterial Pressure (mmHg)	93.24 (13.34)
Systolic Blood Pressure (mmHg)	127.11 (19.19)
Diastolic Blood Pressure (mmHg)	76.31 (11.68)
VO_{2max} (percentile)	40.45
$\leq$ 50%ile	62.4
$>$ 50%ile	37.6%

Method

Participants

Participants included a sample of 224 adults (aged 40+ years) from the publicly available Nathan Kline Institute Rockland Sample (NKI-RS; http://fcon_1000.projects.nitrc.org/indi/enhanced; [37]). The NKI-RS is composed of many studies with the same core protocol. Only data from the latest baseline visit was used for each participant to ensure adequate sample size, as complete follow-up data was only available for a subset of these participants due to active data collection. Use of this data for this project was approved through the exempt review process by the University of Maryland College Park Institutional Review Board. Participants were eligible for inclusion if they were 40 years of age or older, had no self-reported neurological (e.g., Alzheimer's, Parkinson's) or psychiatric disorders (e.g., MDD, PTSD, OCD) and completed cardiorespiratory fitness measures, blood pressure measurements, and neuropsychological testing. Participants were excluded if they did not complete a baseline visit, were younger than 40 years old, or had self-reported neurological or psychiatric disorders Fig. 1. depicts a flowchart for included participants for each model. Demographic statistics are presented in Table 1.

Materials

Cardiorespiratory fitness

Cardiorespiratory fitness (CRF) was measured using a six-minute bike test using a recumbent cycle ergometer (RBK 815, Precor, Woodinville, WA) based on a modified Astrand-Ryhming submaximal cycle ergometer test [4]. The level of resistance was determined by the age and sex of each participant. Participant resting heart rate was obtained prior to the test and during the test using a pulse oximeter on the finger. The participant was instructed to pedal at 70 RPM's for 6 min. Final heart rate was obtained when completed. If the participant failed to complete the full 6 min of pedaling at 70 RPM's, they were not able to be included in the analyses. Estimates of VO_{2max} were then extrapolated using the Astrand nomogram [4,30]. Values falling outside the range of 12.0–90.0 mL·kg-1·min-1 were excluded based on published reference values on VO_{2max} for men and women across relevant age groups [3,26,27]. Only one participant with a very high value (>100 mL·kg-1 min-1) was excluded. Because of the known influence of age and sex on VO_{2max}, estimates of VO_{2max} were standardized and converted into a percentile rank based on age and sex using normative information [3].

Executive function

Each participant received neuropsychological testing as part of a larger cognitive battery. All participants were administered specific subtests of the Delis-Kaplan Executive Function System (DKEFS) including the Trail Making Test, Verbal Fluency, Design Fluency, Color Word Interference, and Tower Test. These tests have good psychometric properties, measure non-verbal and verbal executive function, and have relatively brief administration times [56]. To combine subtests and create composites, z-scores were calculated for each participant [49]. The switching composite category consisted of DKEFS Verbal Fluency Category Switching: Total Switching Accuracy and DKEFS Design Fluency: Switching Total Correct. The planning composite category consisted of TOWER: Total Achievement Total Score and Trails 4: Total Time to Complete. The fluency composite category consisted of Verbal Fluency: Total Letter Fluency for Three Letter Trials and Design Fluency: Total Correct Trials 1–3. The inhibition category consisted of Color Word Inhibition: Total Time to Complete.

Mean arterial pressure

The systolic and diastolic blood pressures were both taken with a mercury blood pressure gage, cuff, and stethoscope at the baseline visit. Mean Arterial Pressure (MAP) is the average arterial pressure throughout one cardiac cycle, systole, and diastole and is a good measure of perfusion [13]. Changes in perfusion pressure, along with changes in vascularity and blood viscosity, affect cerebral blood flow (CBF; [19]). MAP was calculated using Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP). This was calculated as follows: $MAP = ([(DBP \times 2)+SBP]/3)$.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (IBM SPSS Version 25.0) PROCESS Macro [23]. The relation between level of CRF and executive function as mediated through MAP was examined with four separate models for each executive function category (Switching, Planning, Fluency, Inhibition) and unstandardized beta values were calculated through PROCESS. Conceptual and empirical evidence suggests that indirect effects should be examined irrespective of direct effects [46]. All indirect effects were analyzed using bootstrap analyses set at 10,000 samples and a 95% confidence interval [44]. In order to capture the unique relations between CRF, MAP, and executive function, age, sex, and years of education were controlled for in all analyses.

Table 2
Mediation results for the associations between cardiorespiratory fitness, executive function, and mean arterial pressure controlling for age, sex, and education.

Analyses	B	CI	t-value	*p*-value
CRF and MAP	−0.12	[−0.18, −0.07]	−4.43	**<0.00001**
MAP and Inhibition	0.009	[−0.0021, 0.02]	1.59	.11
MAP and Switching	−0.009	[−0.028, 0.0099]	−0.94	.35
MAP and Fluency	−0.023	[−0.042, −0.0038]	−2.37	**.02**
MAP and Planning	−0.031	[−0.049, −0.014]	−3.51	**.0006**
Direct Effect of CRF on Inhibition	−0.0048	[−0.0092, −0.0004]	−2.16	**.03**
Direct Effect of CRF on Switching	0.0064	[−0.0010, 0.0138]	1.71	.09
Direct Effect of CRF on Fluency	0.0015	[−0.0059, 0.009]	0.41	.69
Direct Effect of CRF on Planning	0.0045	[−0.0024, 0.011]	1.29	.20
Mediation Models	**B**	**SE**	**LLCI**	**ULCI**
Indirect Effect of MAP (Inhibition Model)*	−0.0011	0.0006	−0.0026	−0.0002
Indirect Effect of MAP (Switching Model)	0.0011	0.0011	−0.0010	0.0036
Indirect Effect of MAP (Fluency Model)*	0.0028	0.0012	0.0009	0.0053
Indirect Effect of MAP (Planning Model)*	0.0037	0.0015	0.0014	.00074

Significant *p*-values are depicted in bold. * Indicates significant indirect effect.
Note. CI = Confidence Interval, LLCI = Lower Limit Confidence Interval, ULCI = Upper Limit Confidence Interval, CRF = Cardiorespiratory Fitness, MAP = Mean Arterial Pressure.

Results

Descriptive characteristics

Table 1 provides means and standard deviations for sociodemographic characteristics. The average age was 56 years old (SD = 9.05). The majority of the participants were female (72%) and White (84%). On average, participants had completed 16 years (SD = 4.16) of education. The average systolic blood pressure was 127.11 mmHg (SD = 19) and average diastolic blood pressure was 76.31 mmHg (SD = 11.68). The average mean arterial pressure was 93.24 mmHg (SD = 13.34). A small minority of the sample had diabetes (Type 1=<1%; Type 2 = 4.7%). On average, participants were in the 40th percentile for VO_{2max}, indicating that this sample overall had lower than expected fitness. A minority of the participants had self-reported hypertension (21%) or hypotension (11%). Overall, average sample performances on measures of executive function were comparable to normative data on these subtests.

Direct effects and mediation models

The direct effect of CRF on executive function controlling for age, sex, and education was significant for the Inhibition model only ($B = -0.0048$, $t = -2.16$ $p = .03$). In addition, there were significant indirect effects of CRF on Inhibition ($B = -0.0011$, CI = −0.0026, −0.0002),

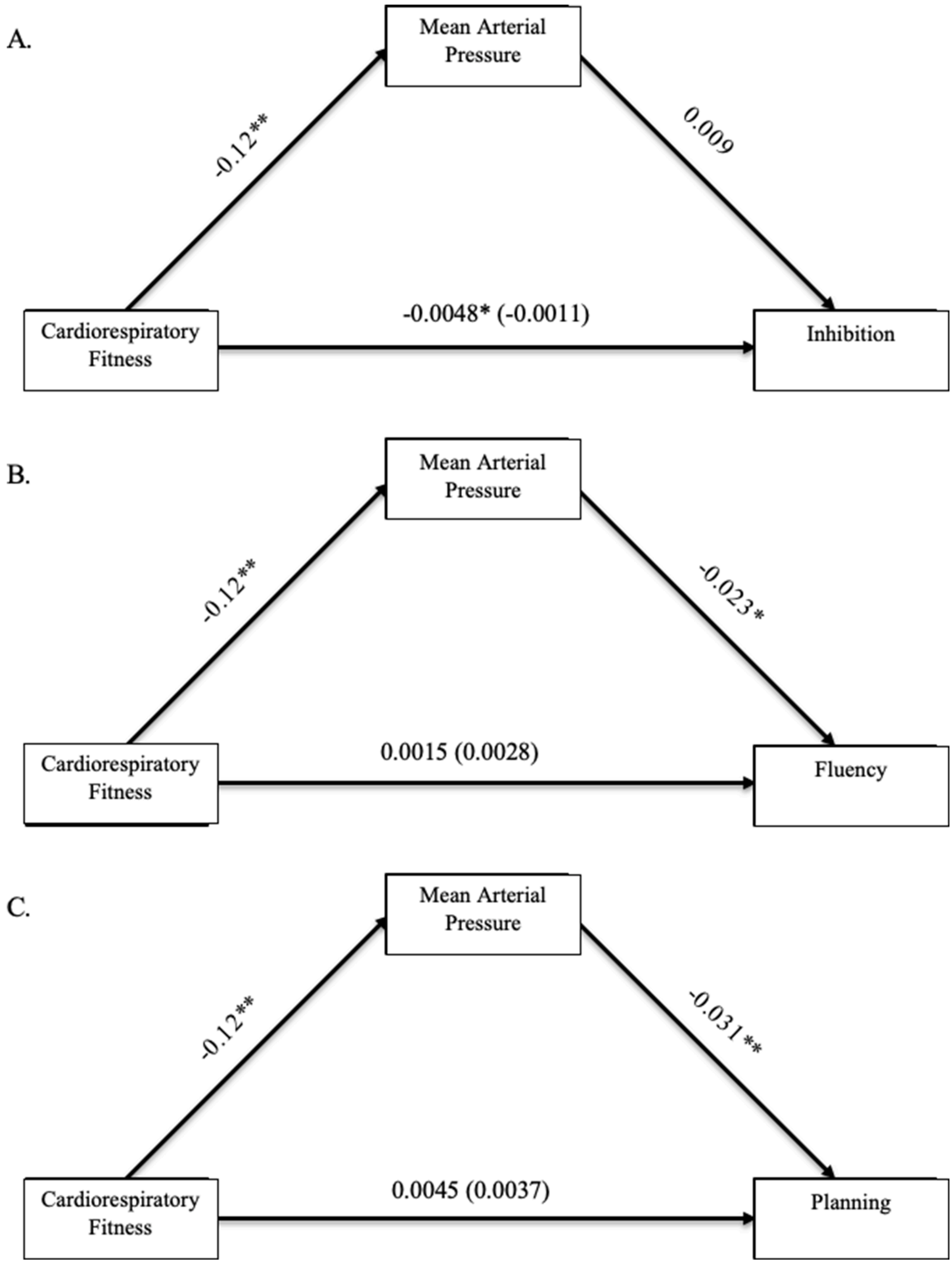

Fig. 2. Mediation models.
Note. Models presented for Inhibition (A), Fluency (B), and Planning (C) with **B** values indicated for each path. Indirect effects are represented in parentheses. $^{*}p <$ .05, $^{**}p <$ .01.

Planning ($B = 0.0037$, CI = 0.0014, 0.00074) and Fluency ($B = 0.0011$, CI = −0.0010, 0.0036) through MAP after controlling for age, sex, and education. There was not a significant indirect effect of CRF on Switching through MAP (see Table 2).

Indirect effects

There were significant associations in the mediation models when controlling for age, sex, and education (see Fig. 2 for mediation model schematic). Greater CRF was significantly associated with lower MAP in all models ($p = < 0.00001$). Greater mean arterial pressure was related to worse fluency ($B = -0.023$, $t = -2.37$, $p = 0.02$) and planning ($B =$

−0.0314, $t = -3.51$, $p = .0006$). There was also a significant direct effect of CRF on inhibition ($B = -0.0048$, $t = -2.16$, $p = .03$; see Table 2).

Discussion

Previous literature indicates that higher CRF is related to better executive function in older adulthood [5,42], but there is less evidence examining the mechanisms underlying this association. The current study sought to examine whether MAP mediated this association in a sample of adults ranging from middle age to older adulthood. We found that while greater CRF was only directly related to better inhibition, there were significant indirect effects of CRF on inhibition, planning, and fluency through MAP. In addition, there were significant associations of CRF and MAP and MAP and executive function composites within the mediation models. These results indicate that CRF may be associated with executive function through MAP in a middle-age to older adult sample. This is significant because it suggests the importance of CRF in regulating MAP earlier in the aging process, and suggests that this modulation may have beneficial effects on cognitive functioning.

Our results showed that there was only a significant direct effect of CRF on executive function in the inhibition model, while the other domains were not significant but were in the expected directions (i.e., greater CRF was associated with better executive function). Perhaps fitness impacts the prefrontal-basal ganglia networks that control inhibitory functions [31] more so than the other networks responsible for other facets of executive function (i.e., planning, fluency, switching). Thus, this might explain why these results only partially supported our hypotheses. Given a relatively younger older adult sample (Mean age = 56), there is some evidence that CRF and physical activity exert less of an influence on cognitive functioning in middle age [48]. This is similar to a recent study that found that in a sample of 501 adults aged 40–65 years, CRF was related to frontal-loading cognitive abilities only in those ≥55 years old [18]. Therefore, we may not have had enough power and age variability in our sample to detect subtle changes in executive function. However, we might expect the positive impacts of CRF on middle age to be cumulative over time, showing the greatest impacts many years later in the aging process [16,55]. Unfortunately, that relationship over time is not captured by our cross-sectional study.

In line with our hypotheses, there were significant indirect effects of greater CRF and better inhibition, fluency, and planning through MAP. In addition, greater CRF was associated with lower MAP in all models. This suggests that better CRF may benefit executive function through lowering the negative impacts of higher MAP on executive function [21]. Perhaps greater CRF confers a protective effect on vasculature and cerebral hemodynamics through upregulation of neuroprotective growth factors (e.g., VEGF, [35]), increased cerebral perfusion [15], as well as its impact on heart health (e.g., decreasing aortic stiffening, and increasing cardiac output and left ventricular ejection fraction; [54]). This protection may then buffer downstream effects of cerebrovascular dysfunction and disruptions in cardiac hemodynamics, which has implications for cognitive function in aging. Greater MAP was also related to worse fluency and planning. These results are in line with a recent systematic review which suggests that systemic arterial hypertension impacts executive function in adults [34]. Taken together, these results suggest the importance of both CRF and maintenance of blood pressure in middle-age and early older adulthood, which is somewhat of a shift from the current literature that is focused much more heavily on older adulthood. Clinical implications include the implementation of aerobic exercise and management of blood pressure as preventative measures to preserve cognitive functioning.

While there are many strengths to this study, there are several limitations that warrant discussion. First, our analyses were constrained by the design of the NKI-RS study. This sample was mostly White and highly educated, which may hinder generalizability. Future participant recruitment should make efforts to include underrepresented groups. In addition, the cross-sectional nature of this analysis limits the causality that can be drawn. Our composite measures consisted of few subtests, with inhibition consisting of a single subtest. Future studies may consider expanding and diversifying examination of executive function. Finally, blood pressure was measured at a single point in time, and research has indicated that this might be less representative of true blood pressure due to outside factors (e.g., the white coat effect; [40]). Future studies may capture multiple collections of blood pressure over time for a more accurate estimate and may consider using more direct measures of cerebrovascular health. In conclusion, our findings indicate that greater CRF is associated with better executive functioning through MAP in a sample of middle-age and younger older adults, suggesting the importance of viewing MAP as underlying physiological mechanism in this association. Further efforts are needed to examine these associations over time and in more diverse populations.

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References

[1] A.J. Alfini, L.R. Weiss, K.A. Nielson, M.D. Verber, J.C Smith, Resting cerebral blood flow after exercise training in mild cognitive impairment, J. Alzheimers Dis. JAD 67 (2) (2019) 671–684, https://doi.org/10.3233/JAD-180728.
[2] American college of sports medicine. Position stand. Physical activity, physical fitness, and hypertension, Med. Sci. Sports Exerc. 25 (10) (1993) i–x.
[3] American College of Sports Medicine, ACSM's Guidelines for Exercise Testing and Prescription, 10th ed., Lippincott Williams & Wilkins, 2018.
[4] P.O. Astrand, I Ryhming, A nomogram for calculation of aerobic capacity from pulse rate during submaximal work, J. Appl. Physiol. 7 (1954) 218–222.
[5] S. Bauermeister, D Bunce, Aerobic fitness and intraindividual reaction time variability in middle and old age, J. Gerontol. Ser. B Psychol. Sci. Soc. Sci. 71 (3) (2016) 431–438, https://doi.org/10.1093/geronb/gbu152.
[6] C.J. Boraxbekk, A. Salami, A. Wåhlin, L Nyberg, Physical activity over a decade modifies age-related decline in perfusion, gray matter volume, and functional connectivity of the posterior default-mode network—a multimodal approach, Neuroimage 131 (2016) 133–141, https://doi.org/10.1016/j.neuroimage.2015.12.010.
[7] A.Z. Burzynska, L. Chaddock-Heyman, M.W. Voss, C.N. Wong, N.P. Gothe, E. A. Olson, A.F Kramer, Physical activity and cardiorespiratory fitness are beneficial for white matter in low-fit older adults, PLoS One 9 (9) (2014), https://doi.org/10.1371/journal.pone.0107413 e107413.
[8] A. Castells-Sánchez, F. Roig-Coll, R. Dacosta-Aguayo, N. Lamonja-Vicente, A. K. Sawicka, P. Torán-Monserrat, M Mataró, Exercise and fitness neuroprotective effects: molecular, brain volume and psychological correlates and their mediating role in healthy late-middle-aged women and men, Front. Aging Neurosci. 13 (2021) 80, https://doi.org/10.3389/fnagi.2021.615247.
[9] S.B. Chapman, S. Aslan, J.S. Spence, L.F. DeFina, M.W. Keebler, N. Didehbani, H Lu, Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging, Front. Aging Neurosci. (5) (2013) 75, https://doi.org/10.3389/fnagi.2013.00075.
[10] F.T. Chen, J.L. Etnier, K.H. Chan, P.K. Chiu, T.M. Hung, Y.K Chang, Effects of exercise training interventions on executive function in older adults: a systematic review and meta-analysis, Sports Med. 50 (2020) 1451–1467, https://doi.org/10.1007/s40279-020-01292-x.
[11] H.C Chui, Subcortical ischemic vascular dementia, Neurol. Clin. 25 (3) (2007), https://doi.org/10.1016/j.ncl.2007.04.003, 717–vi.
[12] V.A. Cornelissen, N.A Smart, Exercise training for blood pressure: a systematic review and meta-analysis, J. Am. Heart Assoc. 2 (1) (2013), e004473, https://doi.org/10.1161/JAHA.112.004473.
[13] D. DeMers, D Wachs, Physiology, Mean Arterial Pressure, StatPearls, 2020 [Internet].
[14] A Diamond, Executive functions, Annu. Rev. Psychol. 64 (2013) 135–168, https://doi.org/10.1146/annurev-psych-113011-143750.
[15] R.J. Dougherty, E.A. Boots, J.B. Lindheimer, A.J. Stegner, S. Van Riper, D. F. Edwards, C.L. Gallagher, C.M. Carlsson, H.A. Rowley, B.B. Bendlin, S. Asthana, B.P. Hermann, M.A. Sager, S.C. Johnson, O.C. Okonkwo, D.B Cook, Fitness, independent of physical activity is associated with cerebral blood flow in adults at risk for Alzheimer's disease, Brain Imaging Behav. 14 (4) (2020) 1154–1163, https://doi.org/10.1007/s11682-019-00068-w.
[16] R.J. Dougherty, E.M. Jonaitis, J.M. Gaitán, S.R. Lose, B.M. Mergen, S.C. Johnson, O.C. Okonkwo, D.B Cook, Cardiorespiratory fitness mitigates brain atrophy and cognitive decline in adults at risk for Alzheimer's disease, Alzheimers Dement. 13 (1) (2021) e12212, https://doi.org/10.1002/dad2.12212 (Amst).

[17] K.I. Erickson, R.L. Leckie, A.M Weinstein, Physical activity, fitness, and gray matter volume, Neurobiol. Aging 35 (2014) S20–S28, https://doi.org/10.1016/j.neurobiolaging.2014.03.034.
[18] G. España-Irla, J. Gomes-Osman, G. Cattaneo, S. Albu, M. Cabello-Toscano, J. Solana-Sanchéz, Á Pascual-Leone, Associations between cardiorespiratory fitness, cardiovascular risk, and cognition are mediated by structural brain health in midlife, J. Am. Heart Assoc. 10 (18) (2021), e020688, https://doi.org/10.1161/JAHA.120.020688.
[19] S. Fantini, A. Sassaroli, K.T. Tgavalekos, J Kornbluth, Cerebral blood flow and autoregulation: current measurement techniques and prospects for noninvasive optical methods, Neurophotonics 3 (3) (2016), 031411, https://doi.org/10.1117/1.NPh.3.3.031411.
[20] D. Ferreira, R. Correia, A. Nieto, A. Machado, Y. Molina, J Barroso, Cognitive decline before the age of 50 can be detected with sensitive cognitive measures, Psicothema 27 (3) (2015) 216–222, https://doi.org/10.7334/psicothema2014.192.
[21] G. Forte, V. De Pascalis, F. Favieri, M Casagrande, Effects of blood pressure on cognitive performance: a systematic review, J. Clin. Med. 9 (1) (2019) 34, https://doi.org/10.3390/jcm9010034.
[22] N.P. Gothe, J. Fanning, E. Awick, D. Chung, T.R. Wójcicki, E.A. Olson, S.P. Mullen, M. Voss, K.I. Erickson, A.F. Kramer, E McAuley, Executive function processes predict mobility outcomes in older adults, J. Am. Geriatr. Soc. 62 (2) (2014) 285–290, https://doi.org/10.1111/jgs.12654.
[23] Hayes, A.F. (2012). PROCESS: a versatile computational tool for observed variable mediation, moderation, and conditional process modeling. http://www.afhayes.com/public/process2012.pdf. Accessed June 20, 2021.
[24] S.M. Hayes, D.H. Salat, D.E. Forman, R.A. Sperling, M Verfaellie, Cardiorespiratory fitness is associated with white matter integrity in aging, Ann. Clin. Transl. Neurol. 2 (6) (2015) 688–698, https://doi.org/10.1002/acn3.204.
[25] A.S. Jackson, X. Sui, J.R. Hébert, T.S. Church, S.N Blair, Role of lifestyle and aging on the longitudinal change in cardiorespiratory fitness, Arch. Intern. Med. 169 (19) (2009) 1781–1787, https://doi.org/10.1001/archinternmed.2009.312.
[26] L.A. Kaminsky, R. Arena, J Myers, Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing: data from the fitness registry and the importance of exercise national database, Mayo Clin. Proc. 90 (11) (2015) 1515–1523, https://doi.org/10.1016/j.mayocp.2015.07.026.
[27] L.A. Kaminsky, M.T. Imboden, R. Arena, J Myers, Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing using cycle ergometry: data from the fitness registry and the importance of exercise national database (FRIEND) registry, Mayo Clin. Proc. 92 (2) (2017) 228–233, https://doi.org/10.1016/j.mayocp.2016.10.003.
[28] M.E. Kelly, D. Loughrey, B.A. Lawlor, I.H. Robertson, C. Walsh, S Brennan, The impact of exercise on the cognitive functioning of healthy older adults: a systematic review and meta-analysis, Ageing Res. Rev. 16 (2014) 12–31, https://doi.org/10.1016/j.arr.2014.05.002.
[29] R.L. Koscik, S.E. Berman, L.R. Clark, K.D. Mueller, O.C. Okonkwo, C.E. Gleason, S. C Johnson, Intraindividual cognitive variability in middle age predicts cognitive impairment 8–10 years later: results from the wisconsin registry for Alzheimer's prevention, J. Int. Neuropsychol. Soc. 22 (10) (2016) 1016–1025, https://doi.org/10.1017/S135561771600093X.
[30] B.J. Legge, E.W Banister, The Astrand-Ryhming momogram revisited, J. Appl. Physiol. 61 (1986) 1203–1209.
[31] O. Levin, Y Netz, Aerobic training as a means to enhance inhibition: what's yet to be studied? Eur. Rev. Aging Phys. Act. 12 (2015) 14, https://doi.org/10.1186/s11556-015-0160-9.
[32] H.F. Lin, L.C. Huang, C.K. Chen, S.H. Juo, C.S Chen, Carotid atherosclerosis among middle-aged individuals predicts cognition: a 10-year follow-up study, Atherosclerosis 314 (2020) 27–32, https://doi.org/10.1016/j.atherosclerosis.2020.10.015.
[33] E.E. Moore, A.L Jefferson, Impact of cardiovascular hemodynamics on cognitive aging, Arterioscler. Thromb. Vasc. Biol. 41 (4) (2021) 1255–1264, https://doi.org/10.1161/ATVBAHA.120.311909.
[34] N.C. Moraes, I. Aprahamian, M.S Yassuda, Executive function in systemic arterial hypertension: a systematic review, Dement. Neuropsychol. 13 (3) (2019) 284–292, https://doi.org/10.1590/1980-57642018dn13-030004.
[35] C. Morland, K.A. Andersson, Ø.P. Haugen, A. Hadzic, L. Kleppa, A. Gille, L. H Bergersen, Exercise induces cerebral VEGF and angiogenesis via the lactate receptor HCAR1, Nat. Commun. 8 (1) (2017) 1–9, https://doi.org/10.1038/ncomms15557.
[36] Mount, C.A., & Das, J.M. Cerebral perfusion pressure. [Updated 2021 Apr 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537271/.
[37] K.B. Nooner, S.J. Colcombe, R.H. Tobe, M. Mennes, M.M. Benedict, A.L. Moreno, M.P. Milham, The NKI-Rockland sample: a model for accelerating the pace of discovery science in psychiatry, Front. Neurosci. 6 (2012) 152, https://doi.org/10.3389/fnins.2012.00152.
[38] J.M. Northey, N. Cherbuin, K.L. Pumpa, D.J. Smee, B Rattray, Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis, Br. J. Sports Med. 52 (3) (2018) 154–160, https://doi.org/10.1136/bjsports-2016-096587.
[39] K. Pantsiou, O. Sfakianaki, V. Papaliagkas, D. Savvoulidou, V. Costa, G. Papantoniou, D Moraitou, Inhibitory control, task/rule switching, and cognitive planning in vascular dementia: are there any differences from vascular aging? Front. Aging Neurosci. 10 (2018) 330, https://doi.org/10.3389/fnagi.2018.00330.
[40] M.R. Pioli, A.M. Ritter, A.P. de Faria, R Modolo, White coat syndrome and its variations: differences and clinical impact, Integr. Blood Press. Control 11 (2018) 73–79, https://doi.org/10.2147/IBPC.S152761.
[41] H. Pentikäinen, T. Ngandu, Y. Liu, K. Savonen, P. Komulainen, M. Hallikainen, H Soininen, Cardiorespiratory fitness and brain volumes in men and women in the FINGER study, Age Ageing 46 (2) (2017) 310–313, https://doi.org/10.1093/ageing/afw191.
[42] H. Pentikäinen, K. Savonen, T. Ngandu, A. Solomon, P. Komulainen, T. Paajanen, R. Antikainen, M. Kivipelto, H. Soininen, R Rauramaa, Cardiorespiratory fitness and cognition: longitudinal associations in the FINGER study, J. Alzheimers Dis. 68 (3) (2019) 961–968, https://doi.org/10.3233/JAD-180897.
[43] I. Peter, G.D. Papandonatos, L.M. Belalcazar, Y. Yang, B. Erar, J.M. Jakicic, G. S Huggins, Genetic modifiers of cardiorespiratory fitness response to lifestyle intervention, Med. Sci. Sports Exerc. 46 (2) (2014) 302, https://doi.org/10.1249/MSS.0b013e3182a66155.
[44] K.J. Preacher, A.F Hayes, SPSS and SAS procedures for estimating indirect effects in simple mediation models, Behav. Res. Methods Instrum. Comput. 36 (2004) 717–731, https://doi.org/10.3758/BF03206553.
[45] R. Ross, S.N. Blair, R. Arena, T.S. Church, J.P. Després, B.A. Franklin, U Wisløff, Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association, Circulation 134 (24) (2016) e653–e699, https://doi.org/10.1161/CIR.0000000000000461.
[46] D.D. Rucker, K.J. Preacher, Z.L. Tormala, R.E Petty, Mediation analysis in social psychology: current practices and new recommendations, Soc. Personal. Psychol. Compass 5 (6) (2011) 359–371, https://doi.org/10.1111/j.1751-9004.2011.00355.x.
[47] L. Sanders, T. Hortobágyi, S. la Bastide-van Gemert, E.A. van der Zee, M van Heuvelen, Dose-response relationship between exercise and cognitive function in older adults with and without cognitive impairment: a systematic review and meta-analysis, PLoS One 14 (1) (2019), e0210036, https://doi.org/10.1371/journal.pone.0210036.
[48] S.A. Schultz, E.A. Boots, R.P. Almeida, J.M. Oh, J. Einerson, C.E. Korcarz, O. C Okonkwo, Cardiorespiratory fitness attenuates the influence of amyloid on cognition, J. Int. Neuropsychol. Soc. 21 (10) (2015) 841–850, https://doi.org/10.1017/S1355617715000843.
[49] M.K. Song, F.C. Lin, S.E. Ward, J.P Fine, Composite variables: when and how, Nurs. Res. 62 (1) (2013) 45–49, https://doi.org/10.1097/NNR.0b013e3182741948.
[50] T. Tarumi, D.I. Dunsky, M.A. Khan, J. Liu, C. Hill, K. Armstrong, K. Martin-Cook, C. M. Cullum, R Zhang, Dynamic cerebral autoregulation and tissue oxygenation in amnestic mild cognitive impairment, J. Alzheimers Dis. JAD 41 (3) (2014) 765–778, https://doi.org/10.3233/JAD-132018.
[51] M.W. Voss, R.S. Prakash, K.I. Erickson, C. Basak, L. Chaddock, J.S. Kim, A. F Kramer, Plasticity of brain networks in a randomized intervention trial of exercise training in older adults, Front. Aging Neurosci. 2 (2010) 32, https://doi.org/10.3389/fnagi.2010.00032.
[52] M.W. Voss, T.B. Weng, A.Z. Burzynska, C.N. Wong, G.E. Cooke, R. Clark, A. F Kramer, Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging, Neuroimage 131 (2016) 113–125, https://doi.org/10.1016/j.neuroimage.2015.10.044.
[53] J. Won, D.D. Callow, G.S. Pena, M.A. Gogniat, Y. Kommula, N.A. Arnold-Nedimala, J.C Smith, Evidence for exercise-related plasticity in functional and structural neural network connectivity, Neurosci. Biobehav. Rev. (2021), https://doi.org/10.1016/j.neubiorev.2021.10.013.
[54] Y. Zhang, L. Qi, L. Xu, X. Sun, W. Liu, S. Zhou, S.E Greenwald, Effects of exercise modalities on central hemodynamics, arterial stiffness and cardiac function in cardiovascular disease: systematic review and meta-analysis of randomized controlled trials, PLoS One 13 (7) (2018), e0200829, https://doi.org/10.1371/journal.pone.0200829.
[55] N. Zhu, D.R. Jacobs, P.J. Schreiner, K. Yaffe, N. Bryan, L.J. Launer, B Sternfeld, Cardiorespiratory fitness and cognitive function in middle age: the CARDIA study, Neurology 82 (15) (2014) 1339–1346, https://doi.org/10.1212/WNL.0000000000000310.
[56] D Delis C, J Kaplan H, E Kaplan, J Holdnack, Reliability and validity of the Delis-Kaplan Executive Function System: an update, Journal of the International Neuropsychological Society 10 (2) (2004) 301–303, https://doi.org/10.1017/S1355617704102191.