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Midlife exercise blood pressure, heart rate, and fitness relate to brain volume 2 decades later

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ABSTRACT

Objective: To determine whether poor cardiovascular (CV) fitness and exaggerated exercise blood pressure (BP) and heart rate (HR) were associated with worse brain morphology in later life.

Methods: Framingham Offspring participants (n = 1,094, 53.9% female) free from dementia and CV disease (CVD) underwent an exercise treadmill test at a mean age of 40 ± 9 years. A second treadmill test and MRI scans of the brain were administered 2 decades later at mean age of 58 ± 8 years.

Results: Poor CV fitness and greater diastolic BP and HR response to exercise at baseline were associated with a smaller total cerebral brain volume (TCBV) almost 2 decades later (all $p < 0.05$) in multivariable adjusted models; the effect of 1 SD lower fitness was equivalent to approximately 1 additional year of brain aging in individuals free of CVD. In participants with prehypertension or hypertension at baseline, exercise systolic BP was also associated with smaller TCBV ($p < 0.05$).

Conclusion: Our results suggest that lower CV fitness and exaggerated exercise BP and HR responses in middle-aged adults are associated with smaller brain volume nearly 2 decades later. Promotion of midlife CV fitness may be an important step towards ensuring healthy brain aging.

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GLOSSARY

BP = blood pressure; **CARDIA** = Coronary Artery Risk Development in Young Adults Study; **CV** = cardiovascular; **CVD** = cardiovascular disease; **DBP** = diastolic blood pressure; **DEC** = duration-based exercise capacity; **ETT** = exercise treadmill test; **HR** = heart rate; **NP** = neuropsychological; **SBP** = systolic blood pressure; **TCBV** = total cerebral brain volume; **WMHV** = white matter hyperintensity volume.

Cardiovascular (CV) fitness is emerging as a factor associated with cognitive health in older age.[1,2] Cross-sectional and short-term (2-year) observational studies have demonstrated that lower fitness levels are associated with increased brain atrophy in patients with Alzheimer disease.[3,4] Similarly, healthy elderly individuals with low fitness have increased cerebral white matter hyperintensity volume (WMHV).[5] A recent study also reported that higher physical fitness levels in middle-aged adults was associated with larger brain volumes 5 years later.[6] Exercise training programs may increase cerebral blood flow and oxygen delivery,[7] improve neuroplasticity, and prevent age-related brain atrophy over the short term,[2,8] but it is not clear whether physical fitness throughout adulthood has an impact on brain aging in later life.

Higher CV fitness may also reduce the impact of vascular risk factors[9,10] that are associated with brain structural abnormalities and cognitive decline.[11,12] Poor CV fitness and vascular dysfunction exaggerate fluctuations in blood pressure (BP) and heart rate (HR) during low-level exercise.[13–15] Therefore, the hemodynamic response to low-level exercise may unmask underlying vascular dysfunction and poor CV fitness. Exaggerated exercise hemodynamics has been associated with target organ damage[16] in relation to CV disease (CVD),[17] but the association of midlife exercise hemodynamics and fitness with late-life brain structure has not

Supplemental data at Neurology.org

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been explored. The objective of the current investigation was to determine whether midlife CV fitness and BP and HR responses to a low-level exercise test were associated with brain morphology in later life.

METHODS

The Framingham Heart Study began in 1948 as a prospective epidemiologic study of CVD.[18] Offspring of the original Framingham cohort (n = 3,548) and spouses of those offspring (n = 1,576) were recruited as part of the Framingham Offspring Study.[19] Offspring Study participants have had regular clinical examinations approximately every 4 years. Between 1979 and 1983, at the second offspring examination (cycle 2), participants completed an exercise treadmill test (ETT). Approximately 2 decades later (during 1998–2001), eligible attendees repeated an abbreviated version of the ETT at cycle 7 and also completed neuropsychological (NP) testing and MRI brain scans at a callback visit shortly thereafter (table e-1 on the *Neurology*® Web site at Neurology.org).

Participants were excluded from the primary analysis (sample 1, described in figure e-1) if they had prevalent CVD, or had been taking β-blockers at cycles 2 or 7 (n = 304), or had clinical dementia, stroke, or other neurologic conditions that could affect the MRI/NP assessment (brain tumor, major head trauma, multiple sclerosis) at cycle 7 (n = 32). Participants were additionally excluded if they were unable to complete stage 2 of the ETT or there were technical problems with the test (n = 29) at either cycle 2 or 7. Overall, 1,199 participants had NP data, whereas 1,094 had brain imaging information. Sample 2 (n = 1583) was a more inclusive sample, used as an attempt to limit the bias due to excessive weighting toward healthier individuals. In sample 2, participants were not excluded if they developed CVD or began taking β-blockers after cycle 2 or had not completed the cycle 7 ETT.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the institutional review board at the Boston University Medical Center, and all participants gave written informed consent.

ETT at baseline (examination cycle 2). The first ETT was performed using the modified Bruce protocol.[20] Briefly, participants warmed up on the treadmill for 6 minutes at 1.7 MPH and 0%–5% grade (stage 0 and ½ of the Bruce protocol). Each subsequent stage lasted 3 minutes: stage 1 (1.7 MPH, 10% grade), stage 2 (2.5 MPH, 12% grade), stage 3 (3.4 MPH, 14% grade), stage 4 (4.2 MPH, 16% grade), and stage 5 (5 MPH, 18% grade). Participants continued exercising until exhaustion (including chest or leg discomfort) or achievement of a target HR based on 85% of age- and sex-predicted maximal HR.[21] Other reasons for termination of the test included angina, ischemic ST segment depression >2 mm, repetitive ventricular ectopy, unexpected drop in systolic BP (SBP), or rise ≥250 mm Hg. BP and HR recorded at rest and at the midpoint of stage 2 were used in the current analysis.

The following steps were completed in order to estimate duration-based exercise capacity (DEC), based on the assumption that HR increases linearly during the Bruce protocol.[22] For participants who reached their target HR (85% maximal predicted HR), regression equations were created by plotting HR at each stage of exercise. These equations were used to extrapolate the duration of the treadmill test that could have been completed at the estimated maximal HR for each individual (DEC). For participants who terminated the treadmill test before achievement of target HR, DEC was defined as the test duration, without extrapolation. DEC was then used in the following equation[20] to calculate estimated exercise capacity (i.e., peak VO_2):

Estimated exercise capacity[20] (mL/kg/min) = 6.7 − 2.83 (1 [men] or 2 [women]) + 0.056 (DEC).

ETT during later life (19 years follow-up, examination cycle 7). Approximately 19 years after the first ETT, the cycle 7 offspring evaluation included an abbreviated ETT. This protocol included a 1-minute warm-up, followed by stage 1 and 2 of the Bruce protocol, described above. Exercise was terminated after completion of stage 2; therefore, estimated exercise capacity could not be calculated at this examination. However, BP and HR measured at rest and at the midpoint of stage 2 (analogous to that at examination cycle 2) were used in our analyses.

Volumetric brain MRI outcomes. Brain MRI (3D T1-and T2-weighted double spin-echo) was obtained on a Siemens (Munich, Germany) 1.5 T scanner, in 4-mm contiguous slices with repetition time 2,420 milliseconds, echo time 1 = 20 milliseconds/echo time 2 = 90 milliseconds, echo train 8 milliseconds, field of view 22 centimeters, matrix 182 × 256 interpolated to 256 × 256 with one excitation.[23,24] Other MRI parameters, descriptions of blinded image analysis, and definitions of brain volumes have been published previously.[23,24] Briefly, total cerebral brain volume (TCBV) was corrected for differences in head size by computing these variables as ratios with respect to total cranial volume (QUANTA 6.2; Sun Microsystems Ultra 5 workstation, Santa Clara, CA). Age was regressed onto brain volume and this relationship was used to estimate the number of years of brain aging associated with specific fitness indices (0.2% TCBV loss was noted per year of aging).[12]

Statistical analysis. We performed univariate analyses to describe baseline characteristics in the sample of participants at midlife (baseline, examination cycle 2: 1979–1983) and at later life (examination cycle 7: 1998–2001) for all nonmissing data, and then used paired *t* tests to compare the clinical characteristics of participants between these time periods. Two primary analyses were conducted for participants with no missing data. First, multivariable-adjusted linear regressions were used to assess relations between each of the CV fitness/exercise hemodynamic (independent) variables at baseline and at follow-up, and our primary dependent brain MRI measure (TCBV) at follow-up, at examination cycle 7. We conducted these analyses in our primary sample (sample 1), and also in a less restrictive sample (sample 2, including participants who developed CVD or began taking β-blockers in the interim between examination cycles 2 and 7, or did not participate in the treadmill test at examination cycle 7). Models were adjusted for age, sex, and time between examination cycle and MRI; model 2 was additionally adjusted for the following covariates at time of ETT: smoking, diabetes, *APOE* ε4 genotype status, and use of antihypertensive medication; and examination cycle 7 models were also adjusted for serum homocysteine (levels were not available at examination cycle 2). Second, a set of analyses was performed using interaction terms to assess effect modification by sex, by hypertension status at baseline (examination cycle 2), and by age at follow-up (examination cycle 7) (<60 vs ≥60 years), and then stratifying analyses by these subgroups if statistically significant interactions were observed. Supplementary methods and analysis are described in appendix e-1. Significance was set at $p < 0.05$ for all 211 models and $p < 0.10$ for analyses assessing effect modification. Analyses were performed using Statistical Analyses System software version 9.3 (SAS Institute, Cary, NC).

RESULTS At baseline, the average age was 40 years (table 1). Prevalence of hypertension presented at the Framingham Heart Study examinations increased from 9% to 28% across the 19-year follow-up period. By the time of examination cycle 7, 60% of participants had either prehypertensive or hypertensive BP. Across the 2-decade observation period, resting and exercise SBP increased, while resting and exercise diastolic BP (DBP) decreased slightly.

CV fitness at baseline (examination cycle 2) and brain structure and function at follow-up (examination cycle 7). In the baseline examination (cycle 2), 89% of participants were able to achieve their target HR (85% of predicted HR maximum) (table 1). The average participant reached stage 4 of the exercise treadmill test, with an estimated exercise capacity equivalent to 39 mL/kg/min. Lower estimated exercise capacity at midlife was associated with smaller TCBV in later life (table 2); an effect size of 1 SD lower exercise capacity was equivalent to greater than 1 year of accelerated brain aging. Additional analysis also showed stronger relations between estimated exercise capacity and TCBV in a less restrictive (sample 2) model (table 2); in this more inclusive study sample, an effect size of 1 SD lower exercise capacity was equivalent to 2 years of brain aging. Lower estimated exercise capacity was also associated with smaller frontal lobe volume in the minimally adjusted model (table e-2), but was not associated with measures of cognitive function (table e-3).

Table 1 Demographic and clinical characteristics of sample 1 across midlife (n = 1,199)

	Cycle 2	Cycle 7	*p* Value
Demographic variables			
Age, y	40 ± 9	58 ± 8	<0.001
Women	646 (53.9)	—	—
APOE ε4 genotype	242 (20.7)	—	—
Plasma total homocysteine level, μmol/L	7.6 (6.3, 9.0)	—	—
Education			
No high school degree	29 (2.42)	—	—
High school	660 (55.05)	—	—
College graduate	510 (42.54)	—	—
Hypertension (stage 1)	109 (9.10)	339 (28.27)	<0.001
Prehypertension or hypertension	465 (38.81)	715 (59.63)	<0.001
Antihypertensive medication	24 (2.0)	212 (17.7)	<0.001
Diabetes mellitus	3 (0.3)	75 (6.4)	<0.001
Current smoking	371 (31.0)	144 (12.0)	<0.001
Resting SBP	116 ± 13	122 ± 16	<0.001
Resting DBP	75 ± 9	74 ± 9	0.001
Resting HR	64 ± 10	66 ± 10	<0.001
Exercise measures			
Stage 2 exercise SBP	155 ± 23	166 ± 25	<0.001
Stage 2 exercise DBP	82 ± 13	74 ± 15	<0.001
Stage 2 exercise HR	132 ± 19	129 ± 19	<0.001
Target HR (85% predicted HR maximum) reached	1,070 (89.24)	—	—
Duration of exercise, min	9.5 ± 2.2	—	—
Estimated exercise capacity, mL/kg/min	39 ± 8	—	—

Abbreviations: DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.
Values are mean ± SD, median (Q1, Q3), or n (%).

Exercise hemodynamics at baseline and follow-up (examination cycles 2 and 7) and brain structure and function at follow-up (examination cycle 7). Greater baseline exercise DBP and HR responses were associated with smaller TCBV in later life in maximally adjusted models (table 2); effect sizes of 1 SD higher exercise DBP or HR were equivalent to approximately 1 year of brain aging. In contrast, higher baseline exercise DBP was associated with better performance on Trail Making Test Part B minus Part A (Trails B − A) test in later life (table e-3).

Many statistically significant interactions were observed among baseline CV fitness and exercise hemodynamic variables and age, sex, and hypertension status in relation to TCBV (table 3). In participants with either prehypertension or hypertension at baseline, exercise SBP was associated with smaller TCBV, even after adjusting for age, sex, and resting SBP. In men, there was also an association between baseline exercise SBP and TCBV. Baseline exercise SBP and DBP were associated with TCBV only in participants >60 years at follow-up; baseline exercise HR and estimated exercise capacity were associated with TCBV only in participants <60 years at follow-up.

Greater baseline exercise HR response was associated with smaller frontal lobe volume in later life (table e-2). Additional analysis also showed significant relations between all of the exercise hemodynamic variables and frontal lobe volume (and exercise DBP with WMHV) in the less restrictive sample 2. In later life, higher exercise HR was associated with smaller TCBV and frontal lobe volume (table e-4). The associations of later life exercise BP with TCBV or frontal lobe volume were attenuated by adjustment for vascular risk factors.

DISCUSSION We describe an association of early midlife CV fitness with later life brain volume in individuals free from CVD, stroke, or dementia. Poor physical fitness in older age has previously been linked to a greater WMHV and a lower parenchymal brain volume in cross-sectional or short (≤5 years) intervention observational studies,[2–6,25] but our study is the first to demonstrate that early midlife

Table 2 Linear regression of total cerebral brain volume measured in later life on fitness and exercise hemodynamic variables at baseline, in sample 1[a] (n = 1,094) and sample 2[b] (n = 1,583)

	Sample 1[a] (n = 1,094)		Sample 2[b] (n = 1,583)	
Variable	β ± SE	*p* Value	β ± SE	*p* Value
Baseline (cycle 2)				
Exercise SBP				
Model 1	−0.08 ± 0.04[c]	0.040[c]	−0.12 ± 0.04[c]	0.0023[c]
Model 2[d]	−0.06 ± 0.05	0.164	−0.10 ± 0.04[c]	0.01[c]
Exercise DBP				
Model 1	−0.15 ± 0.06[c]	0.020[c]	−0.18 ± 0.06[c]	0.0034[c]
Model 2[d]	−0.14 ± 0.07[c]	0.049[c]	−0.17 ± 0.06[c]	0.008[c]
Exercise HR				
Model 1	−0.07 ± 0.04	0.104	−0.09 ± 0.04[c]	0.037[c]
Model 2[d]	−0.12 ± 0.05[c]	0.021[c]	−0.11 ± 0.05[c]	0.024[c]
Estimated exercise capacity				
Model 1	0.02 ± 0.01	0.075	0.05 ± 0.01[c]	<0.0001[c]
Model 2[e]	0.03 ± 0.01[c]	0.027[c]	0.05 ± 0.01[c]	<0.0001[c]

Abbreviations: CVD = cardiovascular disease; DBP = diastolic blood pressure; ETT = exercise treadmill test; HR = heart rate; SBP = systolic blood pressure.
β standardized to 10 mm Hg blood pressure or 10 bpm HR. Model 1: adjusted for age, sex, and time from examination to MRI. Model 2: additionally adjusted for the following baseline (cycle 2) covariates: smoking status, diabetes, *APOE* ε4 genotype, and antihypertensive medication.
[a] Sample 1 excluded participants if they had prevalent CVD, were taking β-blockers at cycle 2 or cycle 7, were unable to complete stage 2 of the ETT at cycle 2 or 7, or had clinical dementia, stroke, or other neurologic conditions at cycle 7.
[b] Sample 2 excluded participants if they had prevalent CVD or were taking β-blockers at cycle 2, were unable to complete stage 2 of the ETT at cycle 2, or had clinical dementia, stroke, or other neurologic conditions at cycle 7. Participants were not excluded if they did not complete the cycle 7 ETT.
[c] Significant β ($p < 0.05$).
[d] Additionally adjusted for resting SBP, DBP, or HR, respectively (at time of ETT).
[e] Additionally adjusted for resting SBP and HR at time of ETT.

CV fitness (mean age 40 years) and BP and HR responses to standardized exercise testing were associated with reduced brain volumes almost 2 decades later. We also provide evidence that the causal pathway linking fitness and exercise hemodynamics to brain morphology may be related to the development of clinical CVD.

Evidence suggests that exercise, which improves fitness levels, influences signaling pathways and the neuroplasticity of the brain, reducing brain atrophy and cognitive decline with age.[26,27] These pathways were not explored in the current investigation. Instead, secondary analysis for this investigation focused on the link between CV fitness and vascular dysfunction. Hypertension and vascular stiffness are risk factors for declining cognitive function[12,28] and have been cross-sectionally associated with larger WMHV[11,12,28–30] and smaller brain volume.[11,31] However, resting measurements of BP and HR do not adequately capture the range of dynamic changes in these variables to which the brain is exposed, in response to stressors (including exercise). It has been postulated that the microvasculature of the brain is particularly vulnerable to the excessive fluctuations in BP,[28] as a consequence of vascular dysfunction[15] and poor CV fitness.[10]

The current investigation revealed that higher DBP response to a submaximal exercise test in midlife was associated with smaller brain volume in later life. This evidence complements previous studies supporting the association between exaggerated exercise BP and target organ damage[16,32] or CV events.[17] These findings should not be interpreted to suggest that exercise is harmful; rather, exercise is the stress that uncovers the vascular dysfunction likely resulting in smaller brain volumes. In contrast, midlife resting BP was not significantly associated with later life TCBV in our cohort (data not shown), although this association has been demonstrated in other cohorts.[29,33] Individuals with exaggerated BP response to low levels of exercise may have vascular dysfunction that may not be discernable with examination of resting BP.[15] There is also growing evidence that ambulatory BP is more strongly associated with functional and structural brain impairments than resting BP measured in a clinical setting.[34,35]

Exercise BP may be an early warning of changes in vascular stiffness that only become evident in later life.[36] Our observed associations between early midlife exercise BP and later life TCBV likely reflects the importance of the duration of exposure to elevated BP levels (which was close to 2 decades in this investigation). Further supportive evidence from our results indicate that later life exercise BP was not associated with brain volume after adjustment for covariates. Midlife hemodynamics may be more representative of the hemodynamics to which the microvasculature in the brain has been exposed over the life course. Later life hemodynamics may also be impacted by a higher rate of concurrent comorbidities, such as occult heart failure or weight loss, which could result in pathologic lowering of BP, thereby confounding the relations between BP and brain aging.[33]

High HR response and low estimated exercise capacity (both markers of poor fitness) were associated with smaller brain volume in models adjusting for risk factors such as diabetes or smoking (which is associated with lower exercise HR [data not shown] and smaller brain volume[12]). Lack of adjustment for potential negative confounders attenuates the apparent effect of fitness on brain morphology. The current investigation also suggests that certain subgroups may have a stronger link between CV fitness, exercise hemodynamics, and brain aging, including individuals at higher risk for developing CVD. In participants

Table 3 Interactions among baseline fitness and exercise hemodynamics variables and age, sex, and hypertension status in relation with later life total cerebral brain volume (sample 1,[a] n = 1,094)

	×HTN status (at baseline [cycle 2])					×Age (at cycle 7)					×Sex				
	INT	Normotensive		PreHTN and HTN		INT	<60 years		>60 years		INT	Male		Female	
	p Value	β ± SE	*p* Value	β ± SE	*p* Value	*p* Value	β ± SE	*p* Value	β ± SE	*p* Value	*p* Value	β ± SE	*p* Value	β ± SE	*p* Value
Exercise SBP[b]	0.005[c]	−0.01 ± 0.06	0.822	−0.13 ± 0.06[c]	0.030[c]	0.002[c]	−0.01 ± 0.05	0.848	−0.12 ± 0.05[c]	0.015[c]	0.095[c]	−0.10 ± 0.05[c]	0.046[c]	−0.07 ± 0.05	0.198
Exercise DBP[b]	0.271	—	—	—	—	0.030[c]	−0.08 ± 0.09	0.381	−0.27 ± 0.11[c]	0.013[c]	0.320	—	—	—	—
Exercise HR[b]	0.091[c]	0.13 ± 0.06[c]	0.032[c]	−0.11 ± 0.08	0.201	0.005[c]	−0.18 ± 0.06[c]	0.005[c]	−0.09 ± 0.07	0.248	0.421	—	—	—	—
Estimated exercise capacity[d]	0.185	—	—	—	—	0.017[c]	0.05 ± 0.02[c]	0.004[c]	0.01 ± 0.02	0.573	0.027[c]	0.04 ± 0.02	0.062	0.02 ± 0.02	0.235

Abbreviations: DBP = diastolic blood pressure; ETT = exercise treadmill test; HR = heart rate; HTN = hypertension; INT = interaction; SBP = systolic blood pressure.
β Standardized to 10 mm Hg BP or 10 bpm HR. Stratified analysis only completed for interactions with a *p* value <0.1. Models adjusted for age, sex, and time from examination to MRI testing.
[a] Sample 1 excluded participants if they had prevalent cardiovascular disease, were taking beta-blockers at cycle 2 or cycle 7, were unable to complete stage 2 of the ETT at cycle 2 or 7, or had clinical dementia, stroke and other neurological conditions at cycle 7.
[b] Additionally adjusted for resting blood pressure, DBP, or HR, respectively (at time of ETT).
[c] Significant β ($p < 0.05$).
[d] Additionally adjusted for resting SBP and HR at time of ETT.

with baseline prehypertension/hypertension, the association between exercise SBP and brain volume was stronger, reaching statistical significance. These results, although observational, suggest that improvements in CV fitness, which lower the exercise BP response, may be particularly beneficial for those with prehypertension or hypertension. Pharmaceutical treatment of hypertension in older age has failed to show prevention of brain volume loss.[37] But earlier interventions to address modifiable risk factors are becoming more attractive. While not yet studied on a large scale, there is evidence to suggest that treatment of BP in midlife may prevent cognitive decline in later life.[38]

The strength of our investigation is the availability of a midlife exercise test that was also repeated similarly in later life (yielding 2 time points of evaluation) in a large community-based sample of healthy adults, free of CVD and dementia. However, due to this design and potential loss to follow-up, our primary dataset (sample 1) may be excessively weighted towards healthier individuals. Strict exclusions were necessary to reduce confounding by comorbidities, but, as presented in sample 1, our results may only be applicable to individuals with otherwise healthy aging. Removal of the individuals at the highest risk may have reduced the effect sizes and our sensitivity to detect associations due to the strong reported relationship between CVD and brain structural abnormalities and cognitive decline. This hypothesis was strengthened by our results in sample 2, demonstrating that our results were stronger in models that were less restrictive (including participants who developed CVD or began taking β-blockers).

Lack of associations in our investigation between CV fitness and cognitive function may be explained by an average age of only 58 years at the later life time point. Detectable cognitive impairment can actually take up to a decade longer than subtle structural brain changes.[39] On the other hand, despite investigating an even younger cohort, a report from the Coronary Artery Risk Development in Young Adults Study (CARDIA) study observed that physical fitness in early adulthood (mean age 25 years) was associated with cognition in later life (mean age 49 years).[1] We are unable to account for the differences between our results and the results from the CARDIA study, except that different age groups and cognitive tests (list learning, digit-symbol, and Stroop) were examined; these tests were not administered to Framingham participants. Our investigation did, however, uncover a stronger relationship between lower CV fitness and smaller brain volume in a subgroup of participants <60 years old at examination cycle 7. Therefore, it is conceivable that the effects of lower CV fitness may be more discernible in early adulthood.

Our findings warrant confirmation in future investigations. We did not account for multiple statistical testing; further, the largely homogenous racial profile (white individuals of European ancestry) of the Framingham Offspring Study decreases the generalizability of our findings to other racial and ethnic groups. Finally, brain MRI measures were only available in later life, thereby hampering our ability to evaluate change in brain volumes over time (between examinations 2 and 7).

Our investigation provides new evidence that lower CV fitness and elevated exercise BP and HR responses in early to midlife are associated with smaller brain volumes nearly 2 decades later, thereby linking fitness over the life course to brain health in later life.[11] Promotion of midlife CV fitness may be an important step towards ensuring healthy brain aging in the population, especially in prehypertensive or hypertensive individuals.

AUTHOR CONTRIBUTIONS

Drs. Seshadri and Beiser had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Drs. Spartano, Himali, Beiser, Vasan, and Seshadri each contributed to the design and conceptualization of the study. Analysis and interpretation of the data: Drs. Spartano, Himali, Beiser, Lewis, Vasan, and Seshadri. Drafting of the manuscript: Drs. Spartano and Himali. Critical revision of the manuscript: All authors.

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REFERENCES

1. Zhu N, Jacobs DR Jr, Schreiner PJ, et al. Cardiorespiratory fitness and cognitive function in middle age: the CARDIA study. Neurology 2014;82:1339–1346.
2. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Science 2003;14:125–130.
3. Vidoni ED, Honea RA, Billinger SA, Swerdlow RH, Burns JM. Cardiorespiratory fitness is associated with atrophy in Alzheimer's and aging over 2 years. Neurobiol Aging 2012;33:16241632.
4. Burns JM, Cronk BB, Anderson HS, et al. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. Neurology 2008;71:210–216.
5. Sen A, Gider P, Cavalieri M, et al. Association of cardiorespiratory fitness and morphological brain changes in the elderly: results of the Austrian Stroke Prevention Study. Neurodegener Dis 2012;10:135–137.
6. Zhu N, Jacobs DR Jr, Schreiner PJ, et al. Cardiorespiratory fitness and brain volume and white matter integrity: the CARDIA Study. Neurology 2015;84:2347–2353.
7. Rogers RL, Meyer JS, Mortel KF. After reaching retirement age physical activity sustains cerebral perfusion and cognition. J Am Geriatr Soc 1990;38:123–128.
8. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci USA 2011;108:3017–3022.
9. Quan HL, Blizzard CL, Sharman JE, et al. Resting heart rate and the association of physical fitness with carotid artery stiffness. Am J Hypertens 2014;27:65–71.
10. Kokkinos P, Pittaras A, Manolis A, et al. Exercise capacity and 24-h blood pressure in prehypertensive men and women. Am J Hypertens 2006;19:251–258.
11. Tsao CW, Seshadri S, Beiser AS, et al. Relations of arterial stiffness and endothelial function to brain aging in the community. Neurology 2013;81:984–991.
12. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology 2011;77:461–468.
13. Mundal R, Kjeldsen SE, Sandvik L, Erikssen G, Thaulow E, Erikssen J. Predictors of 7-year changes in exercise blood pressure: effects of smoking, physical fitness and pulmonary function. J Hypertens 1997;15:245–249.
14. Nauman J, Aspenes ST, Nilsen TI, Vatten LJ, Wisloff U. A prospective population study of resting heart rate and peak oxygen uptake (the HUNT Study, Norway). PLoS One 2012;7:e45021.
15. Thanassoulis G, Lyass A, Benjamin EJ, et al. Relations of exercise blood pressure response to cardiovascular risk factors and vascular function in the Framingham Heart Study. Circulation 2012;125:2836–2843.
16. Gottdiener JS, Brown J, Zoltick J, Fletcher RD. Left ventricular hypertrophy in men with normal blood pressure: relation to exaggerated blood pressure response to exercise. Ann Intern Med 1990;112:161–166.
17. Lewis GD, Gona P, Larson MG, et al. Exercise blood pressure and the risk of incident cardiovascular disease (from the Framingham Heart Study). Am J Cardiol 2008;101:1614–1620.
18. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health Nations Health 1951;41:279–281.
19. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families: The Framingham Offspring Study. Am J Epidemiol 1979;110:281–290.
20. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973;85:546–562.
21. Sheffield LT. Graded exercise tests for ischemic heart disease. In: Exercise Testing and Training of Apparently Healthy Individuals: A Handbook for Physicians. Dallas: American Heart Association; 1975:35–38.

22. Fletcher GF, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards: a statement for health professionals from the American Heart Association. Circulation 1990;82:2286–2322.
23. DeCarli C, Maisog J, Murphy DG, Teichberg D, Rapoport SI, Horwitz B. Method for quantification of brain, ventricular, and subarachnoid CSF volumes from MR images. J Comput Assisted Tomogr 1992;16:274–284.
24. DeCarli C, Massaro J, Harvey D, et al. Measures of brain morphology and infarction in the Framingham Heart Study: establishing what is normal. Neurobiol Aging 2005;26:491–510.
25. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2010;341:c3666.
26. Hotting K, Roder B. Beneficial effects of physical exercise on neuroplasticity and cognition. Neurosci Biobehav Rev 2013;37:2243–2257.
27. Lista I, Sorrentino G. Biological mechanisms of physical activity in preventing cognitive decline. Cell Mol Neurobiol 2010;30:493–503.
28. Mitchell GF, van Buchem MA, Sigurdsson S, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility–Reykjavik study. Brain 2011;134:3398–3407.
29. DeCarli C, Miller BL, Swan GE, et al. Predictors of brain morphology for the men of the NHLBI twin study. Stroke 1999;30:529–536.
30. Poels MM, Zaccai K, Verwoert GC, et al. Arterial stiffness and cerebral small vessel disease: the Rotterdam Scan Study. Stroke 2012;43:2637–2642.
31. Harris P, Alcantara DA, Amenta N, et al. Localized measures of callosal atrophy are associated with late-life hypertension: AGES-Reykjavik Study. Neuroimage 2008;43:489–496.
32. Lauer MS, Okin PM, Anderson KM, Levy D. Impact of echocardiographic left ventricular mass on mechanistic implications of exercise testing parameters. Am J Cardiol 1995;76:952–956.
33. Heijer T, Skoog I, Oudkerk M, et al. Association between blood pressure levels over time and brain atrophy in the elderly. Neurobiol Aging 2003;24:307–313.
34. Wolfson L, Wakefield DB, Moscufo N, et al. Rapid buildup of brain white matter hyperintensities over 4 years linked to ambulatory blood pressure, mobility, cognition, and depression in old persons. J Gerontol A Biol Sci Med Sci 2013;68:1387–1394.
35. Hara A, Tanaka K, Ohkubo T, et al. Ambulatory versus home versus clinic blood pressure: the association with subclinical cerebrovascular diseases: the Ohasama Study. Hypertension 2012;59:22–28.
36. Singh JP, Larson MG, Manolio TA, et al. Blood pressure response during treadmill testing as a risk factor for new-onset hypertension: the Framingham Heart Study. Circulation 1999;99:18311836.
37. Jennings JR, Mendelson DN, Muldoon MF, et al. Regional grey matter shrinks in hypertensive individuals despite successful lowering of blood pressure. J Hum Hypertens 2012;26:295–305.
38. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:2672–2713.
39. Teipel SJ, Grothe M, Lista S, Toschi N, Garaci FG, Hampel H. Relevance of magnetic resonance imaging for early detection and diagnosis of Alzheimer disease. Med Clin N Am 2013;97:399–424.