Prospective Analysis of Leisure-Time Physical Activity in Midlife and Beyond and Brain Damage on MRI in Older Adults

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Abstract

Objective

To test the hypothesis that greater levels of leisure-time moderate to vigorous intensity physical activity (MVPA) in midlife or late life are associated with larger gray matter volumes, less white matter disease, and fewer cerebrovascular lesions measured in late life, we utilized data from 1,604 participants enrolled in the Atherosclerosis Risk in Communities study.

Methods

Leisure-time MVPA was quantified using a past-year recall, interviewer-administered questionnaire at baseline and 25 years later and classified as none, low, middle, and high at each time point. The presence of cerebrovascular lesions, white matter hyperintensities (WMH), white matter integrity (mean fractional anisotropy [FA] and mean diffusivity [MD]), and gray matter volumes were quantified with 3T MRI in late life. The odds of cerebrovascular lesions were estimated with logistic regression. Linear regression estimated the mean differences in WMH, mean FA and MD, and gray matter volumes.

Results

Among 1,604 participants (mean age 53 years, 61% female, 27% Black), 550 (34%), 176 (11%), 250 (16%), and 628 (39%) reported no, low, middle, and high MVPA in midlife, respectively. Compared to no MVPA in midlife, high MVPA was associated with more intact white matter integrity in late life (mean FA difference 0.13 per SD [95% confidence interval (CI) 0.004, 0.26]; mean MD difference −0.11 per SD [95% CI −0.21, −0.004]). High MVPA in midlife was also associated with a lower odds of lacunar infarcts (odds ratio 0.68, 95% CI 0.46, 0.99). High MVPA was not associated with gray matter volumes. High MVPA compared to no MVPA in late life was associated with most brain measures.

Conclusion

Greater levels of physical activity in midlife may protect against cerebrovascular sequelae in late life.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AD = Alzheimer disease; **ARIC** = Atherosclerosis Risk in Communities; **ARIC-NCS** = Atherosclerosis Risk in Communities–Neurocognitive Study; **BMI** = body mass index; **CI** = confidence interval; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FLAIR** = fluid-attenuation inversion recovery; **LTPA** = leisure-time physical activity; **MD** = mean diffusivity; **MET** = metabolic equivalent of task; **MVPA** = moderate to vigorous physical activity; **OR** = odds ratio; **RCT** = randomized controlled trial; **ROI** = region of interest; **WM** = white matter; **WMH** = white matter hyperintensity.

Physical activity is amenable to intervention, but more evidence is needed on the role of an active lifestyle across the life course on brain aging. Our prior work suggests that compared to no physical activity in midlife, moderate/high levels of physical activity were associated with less cognitive decline and a lower incidence of dementia.[1] Pathways that link physical activity to brain-related outcomes have been examined in animal studies and small-scale exercise interventions in humans, but whether these hypothesized pathways apply to community-dwelling populations is unknown.

Both neurodegenerative and cerebrovascular diseases cause reductions in brain volume and white matter (WM) changes.[2] Cerebrovascular disease also causes ischemic lesions.[2] Brain benefits of physical activity have been evaluated in randomized controlled trials (RCTs), mostly acute exercise interventions in controlled settings with relatively small sample sizes,[3,4] but have not been as widely studied in relation to physical activity at the population level. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER, n = 1,260),[5] a recent multicenter RCT of a multimodal intervention, reported better cognition, but no differences in regional brain volumes, cortical thickness, or WM lesions between the intervention and control groups.[6] RCTs of physical activity, in general, have shown mixed results,[7–9] although most were short (~6 months) and typically enrolled older adults with mild cognitive impairment. For practical reasons, most trials only provide snapshots of assigned physical activity and are not reflective of the natural progression of life course physical activity. Therefore, observational studies with repeat physical activity measures are needed to elucidate the long-term role of physical activity on brain structure. We tested the hypothesis that greater leisure-time physical activity in midlife and late life are associated with lower brain pathology burden.

Methods

Study Population and Design

Atherosclerosis Risk in Communities (ARIC) is a community-based prospective cohort study of 15,792 participants aged 45–64 years enrolled from 4 US communities (Washington County, MD; Forsyth County, NC; suburban Minneapolis, MN; and Jackson, MS) in 1987–1989.[10] This analysis included participants who attended the fifth examination (2011–2013), the ARIC-Neurocognitive Study (ARIC-NCS), and received a brain MRI scan (n = 1,963). In comparison to participants who were lost to follow-up or died by the time of visit 5 (2011–2013), those participants who attended the visit had a higher baseline (1987–1989) education and income and lower prevalence of diabetes, hypertension, smoking, and cardiovascular disease (data not shown). As previously described,[2] participants were recruited to have an MRI if they previously participated in the ARIC brain MRI ancillary study (2004–2006)[11] or had evidence of cognitive impairment at the time of their visit 5 examination.[2] A random sample of the remaining participants considered cognitively normal was included. The mean age of participants at the time of MRI acquisition was 76.2 years (SD 5.3). The participants who were selected to undergo MRI were older and (by design) more often of Black race. They also had a slightly lower body mass index (BMI), were less likely to be ever smokers, and had a lower prevalence of coronary heart disease. No differences in sex, education, prevalent diabetes, prevalent hypertension, or physical activity levels were observed between participants who did and did not receive an MRI at the ARIC visit 5 examination (data not shown).

Only participants who attended the visit 5 examination (n = 6,538) were included in this analysis (figure 1). Non-Black/non-White participants and Black participants from Minnesota and Maryland were excluded due to small numbers. We additionally excluded participants who did not receive an MRI or had incomplete MRI data (i.e., poor image quality or missing MRI measures), missing data on self-reported physical activity at the fifth examination and prior visits, a positive or missing dementia diagnosis, or missing covariates. Thus, 1,604 participants were included in our analytic sample.

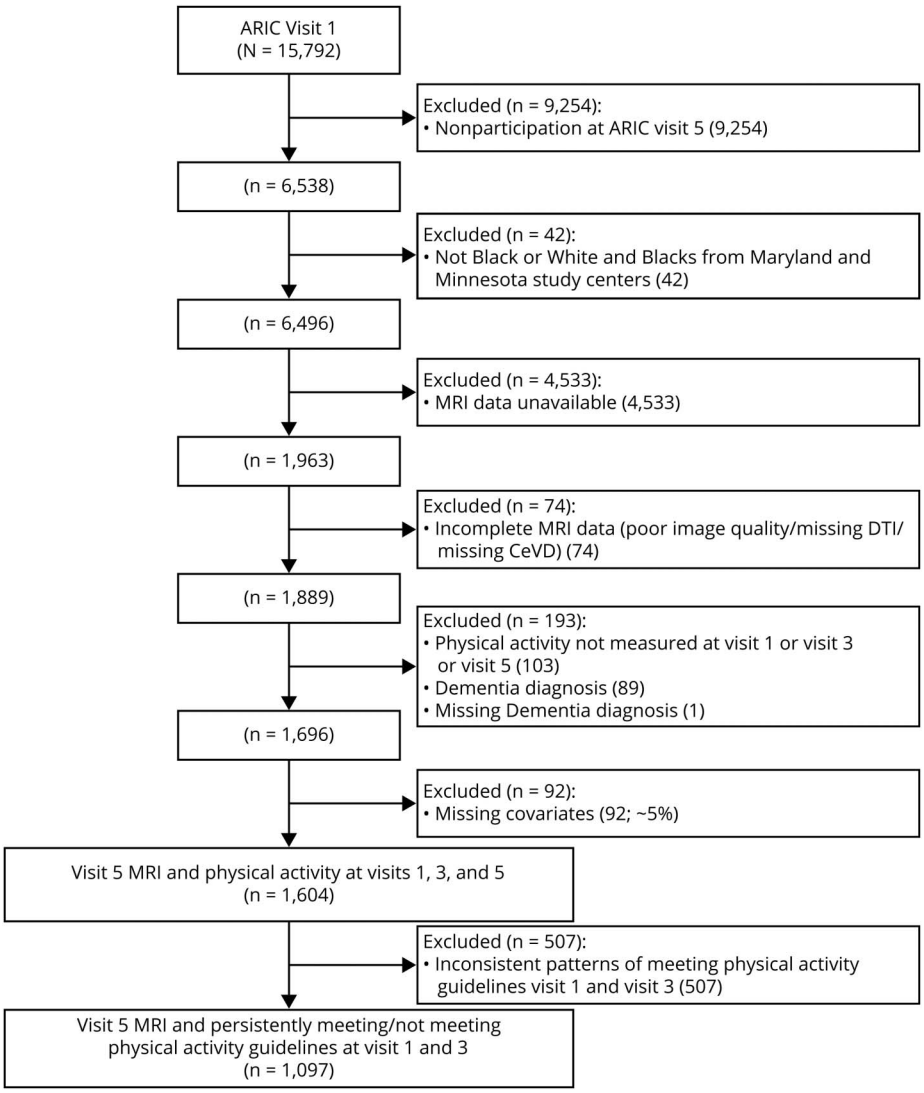
Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the institutional review board at each participating center. Informed consent was obtained from all participants.

Exposure: Leisure-Time Physical Activity (LTPA)

The Modified Baecke Physical Activity Questionnaire was used to measure LTPA at ARIC visits 1 (1987–1989), 3 (1993–1995), and 5 (2011–2013).[12,13] The Baecke Questionnaire is a standardized interviewer-administered questionnaire that asks participants to report on their physical activity over the past year. Summary index scores for sport, leisure, and work activity domains are independently estimated from the questionnaire and range in score from 1 to 5 (reflecting the highest activity level).[12] For the sports domain,

Figure 1 Flow Chart of Study Exclusions and Analytic Sample



ARIC = Atherosclerosis Risk in Communities; CeVD = cerebrovascular disease; DTI = diffusion tensor imaging.

the questionnaire asked participants to list, in open-ended form, up to 4 sports or exercise types in which they engaged. Participants were asked to report on the duration (h/wk) and frequency (number of weeks/mo) for each activity type. These reported activities were assigned metabolic equivalent of task (MET) values, reflecting the intensity of activity, and multiplied with frequency and duration to obtain MET minutes per week (MET·min·wk^{-1}). The metric of MET·min·wk^{-1} was used because it provided a physiologically meaningful estimate that is also comparable to what is reported in other studies. It also allows for classifying participants according to meeting (or not meeting) the recommended levels of physical activity.[14,15]

The assigned MET value ranged from 1–12 METs based on the 2011 Compendium of Physical Activities.[16] For each intensity category (light [1–3 METs], moderate [>3–6 METs], moderate to vigorous [MVPA; >3 METs], and vigorous [>6 METs]), min·wk^{-1} of activity was estimated over the past year by multiplying the frequency and duration, and then summed across all activity types reported within that intensity category, to quantify LTPA by intensity category. A value of 0 minutes·wk^{-1} was assigned to participants who reported not participating in any sports or exercise in the past year. Participants were also categorized as meeting or not meeting the 2008/18 US Physical Activity Guidelines of at least 150 minutes of MVPA intensity per week using LTPA in min·wk^{-1} and intensity based on reported activities of at least 3 METs.[14,15] For this analysis, we operationalized physical activity as (1) categories of min/wk of MVPA in midlife identified as no physical activity (0 min·wk^{-1}), low (1–74 min·wk^{-1}), middle (75–149 min·wk^{-1}), and high (≥150 min·wk^{-1}); and (2) meeting 2008/18 US Physical Activity Guidelines (yes/no). Physical activity was operationalized both in midlife (1987–1989) and at late life (2011–2013), which was concurrent with the brain imaging. Persistent levels

of meeting 2008/18 physical activity guidelines in midlife were identified among those who reported either meeting or not meeting guidelines at both ARIC visits 1 and 3 (n = 1,097, figure 1).

The Baecke Physical Activity Questionnaire has moderate to good reliability (test–retest reliability ranging from 0.74 to 0.88).[12] The questionnaire has also been shown to have moderate validity (Spearman correlation coefficient 0.54) against energy expenditure measured with doubly labeled water.[17] Several strengths of the questionnaire have been identified, including ease of administration, high reliability, and assessment of light to vigorous intensity physical activities that are not well-captured by other self-reported questionnaires.[13] Modified versions of the Baecke Physical Activity Questionnaire have been used in several population-based studies, including the Study of Women's Health Across the Nation and the Jackson Heart Study.[18–20]

Outcome: Structural Brain MRI Measures

Brain MRIs were obtained from a 3T MRI scan at visit 5/ARIC-NCS (2011–2013) and processed at the Mayo Clinic Alzheimer's and Dementia Research Lab.[2] Freesurfer (version 5.1)[21] software was used to calculate regional cortical volumes, reported in cm^3. Analyses were categorized according to the following: cerebrovascular lesions, WM disease, WM integrity, and gray matter volumes. Cerebrovascular lesions included brain infarcts (cortical and lacunar) and subcortical microhemorrhages. Brain infarcts were identified, counted, and measured by a trained imaging technician and confirmed by radiologists. They were then classified as lacunar or cortical infarcts on T2-weighted fluid-attenuation inversion recovery (FLAIR) images. Lacunar infarcts were defined as subcortical T2 FLAIR lesions with central hypointensity >3 mm and hyperintensity ≤20 mm in maximum dimension located in the caudate, lenticular nucleus, internal capsule, thalamus, brainstem, deep cerebral WM, centrum semiovale, or corona radiata.[22,23] Subcortical (subcortical or periventricular) microhemorrhages were also confirmed by a trained imaging technician and identified as lesions on T2* gradient-recalled echo sequences of ≤5 mm in maximum diameter.[23] WM disease was determined from WM hyperintensity (WMH) burden, reported in cm^3, and estimated from an algorithm developed at the Mayo Clinic, Rochester.[24,25] Diffusion tensor imaging (DTI) was used to assess WM integrity by estimating fractional anisotropy (FA) and mean diffusivity (MD). Measures of gray matter volumes included the total cortical (sum of the frontal, parietal, temporal, and occipital lobe volumes), the Alzheimer disease (AD) signature region (combined volume of the parahippocampal, entorhinal, inferior parietal lobules, hippocampus, and precuneus[26]), and deep gray matter volumes. The volumetric data were standardized according to the mean and SD of the analytic sample. All volumetric analyses (total cortical, AD signature, deep gray matter, and WMH volumes) were adjusted for total intracranial volume as a covariate to account for differences in participant head size.

The microstructural integrity of lobar and deep WM regions was quantified by DTI measures of FA and MD, and have been previously described.[27] FA is a unitless measure of the directional constraint of water diffusion and ranges from 0 to 1. MD is a scalar measure of how quickly water molecules diffuse overall (mm^2/s). Worse WM microstructural integrity is indicated by lower FA and higher MD. WM FA and MD were calculated for brain regions defined by an in-house atlas of lobar and deep WM regions based on the STAND400 template.[27,28] The WM regions were intersected with tissue segmentations from each participant's T1-weighted and FLAIR images. Voxels with a >50% probability of being WM were used to calculate WM FA and MD. The segmentation accounts for WMHs in the calculation of WM. Imperfect registration between the DTI and T1-weighted images is a possibility and was accounted for by applying an upper cutoff of MD <0.002 mm^2/s to exclude edge voxels that were primarily CSF. The left and right WM FA and MD were averaged across atlas regions. A weighted average was then estimated, with weights based on the number of voxels in each WM region, to create WM FA and MD measures for 6 regions of interest (ROIs): frontal, temporal, occipital, and parietal lobes and anterior and posterior corpus callosum. An overall measure was derived as the weighted average of these 6 ROIs. FA and MD were standardized to the mean and SD of the analytic sample.

Covariates

Covariates included age, sex, education (less than high school, high school or equivalent, and greater than high school), field center–race (Minnesota White; Maryland White; North Carolina White; North Carolina Black; Mississippi Black), *APOE* ε4 genotype (0 or ≥1 allele), and smoking (ever vs never). All covariates, except age and smoking, which were included at the time of the physical activity assessment, were assessed at the baseline ARIC visit. Sensitivity analyses considered adjustment for concurrent cardiovascular and lifestyle risk factors measured at the time of the fifth examination (2011–2013): diabetes mellitus (defined as fasting glucose ≥126 mg/dL or ≥200 mg/dL nonfasting glucose, self-reported history of physician-diagnosed diabetes, or use of diabetes medication); hypertension (defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of blood pressure–lowering medication); and BMI (calculated as measured weight in kilograms divided by height in meters squared).

Statistical Analysis

Descriptive analysis used χ^2 and analysis of variance tests to examine differences in baseline demographic and disease characteristics according to categories of MVPA in midlife. Multivariable logistic regression was used to estimate the associations of physical activity, measured in midlife (visit 1, 1987–1989) and late life (visit 5, 2011–2013), with the odds of cortical or lacunar infarcts and subcortical microhemorrhages across categories of MVPA, in reference to the lowest category (no physical activity). We used multivariable

linear regression models to estimate the mean differences in FA, MD, and log-transformed volumes of WMH, and total cortical, AD signature region, and deep gray matter volumes. Models were adjusted for age, sex, education, race–ARIC field center, *APOE* ε4, and ever smoking. We additionally adjusted for intracranial volume in analyses of volumetric outcomes. A *p* trend was estimated using category number as a continuous variable. Additional sensitivity analyses examined BMI, hypertension, diabetes, and stroke as confounders. Incident strokes (n = 39), adjudicated according to hospital reports of discharge diagnoses that included a cerebrovascular disease code or procedure, were also excluded in a sensitivity analysis. All analyses were weighted to account for the stratified random sampling approach used to select persons to receive an MRI and therefore weighted back to the sample of ARIC participants who attended visit 5. Stata version 15.0 was used for all analyses (StataCorp LLC, College Station, TX).

Data Availability

Researchers can obtain ARIC data from the NIH public data repository (BioLINCC, biolincc.nhlbi.gov/studies/aric/) by signing a data use agreement.

Results

Participant Characteristics

Demographic and clinical characteristics of the study sample (n = 1,604) are provided in table 1 by reported MVPA in midlife (1987–1989). In midlife, 550 (34%), 176 (11%), 250 (16%), and 628 (39%) reported no, low, middle, and high MVPA, respectively. Participants who reported not participating in physical activity were more often Black and female and had lower educational attainment. These participants also had a worse cardiometabolic risk factor profile, including a greater prevalence of hypertension and diabetes. A total of 628 (42.5%) participants met the 2008/18 Physical Activity Guidelines for Americans in midlife. Among the 1,604 participants at baseline, 1,097 (68.4%) had persistent patterns in meeting physical activity guidelines at visits 1 (1987–1989) and 3 (1993–1995). Among the 1,097 participants with persistent patterns of meeting physical activity guidelines at visits 1 and 3, participants were grouped according to persistently meeting (n = 391 [35.6%]) or persistently not meeting (n = 706 [64.4%]) the 2008/18 Physical Activity Guidelines at visits 1 and 3.

Table 1 Weighted[a] Midlife Participant Characteristics Across Categories of Leisure-Time Moderate to Vigorous Physical Activity (MVPA) in Midlife (Visit 1: 1987–1989), n = 1,604

	Leisure-time MVPA in midlife visit 1 (1987–1989), n = 1,604				Persistently meeting physical activity guidelines visit 1 (1987–1989) to visit 3 (1993–1995), n = 1,097	
Midlife visit 1 (1987–1989) participant characteristics	**None (0 min/wk), n = 550**	**Low (1–74 min/wk), n = 176**	**Middle (75–149 min/wk), n = 250**	**High (≥150 min/wk), n = 628**	**Not persistently meeting 2008/18 guidelines, n = 706**	**Persistently meeting 2008/18 guidelines, n = 391**
Age, y, mean (SD)	51.6 (5.2)	51.3 (4.9)	51.5 (5.3)	51.7 (5.0)	51.2 (5.0)	52.0 (5.2)
Female sex	359 (67.7)	113 (61.8)	162 (66.4)	337 (55.6)	476 (67.7)	195 (52.8)
Black race	236 (34.0)	52 (22.5)	55 (15.9)	93 (10.8)	260 (27.9)	56 (10.7)
< High school education	113 (18.6)	26 (11.4)	26 (8.5)	42 (6.1)	126 (15.2)	9 (2.2)
Current smoker	107 (21.4)	36 (22.7)	37 (14.4)	74 (11.0)	126 (18.0)	47 (9.9)
BMI, kg/m, mean (SD)	27.7 (5.8)	26.6 (4.7)	26.3 (4.4)	26.2 (4.4)	27.4 (5.4)	25.8 (4.1)
CHD	5 (0.7)	2 (2.2)	3 (1.3)	5 (0.9)	9 (1.5)	4 (0.7)
Diabetes	39 (6.8)	6 (2.1)	10 (3.1)	25 (4.3)	40 (4.7)	15 (4.2)
Hypertension	176 (28.1)	46 (19.6)	56 (19.7)	100 (14.9)	206 (24.9)	63 (14.3)
≥1 *APOE* ε4 allele	156 (27.7)	52 (25.1)	64 (26.8)	181 (27.1)	198 (26.5)	116 (27.9)
MCI	202 (25.0)	57 (19.0)	95 (24.2)	218 (20.0)	269 (24.9)	136 (20.3)
Cortical infarcts	63 (10.0)	19 (11.9)	22 (7.6)	60 (8.7)	80 (10.1)	43 (10.0)
Lacunar infarcts	113 (18.8)	35 (17.3)	40 (14.7)	97 (13.6)	143 (18.6)	50 (12.9)
Subcortical microhemorrhage	116 (19.8)	41 (23.4)	42 (14.6)	114 (15.9)	152 (19.5)	73 (16.3)

Abbreviations: BMI = body mass index; CHD = coronary heart disease; MCI = mild cognitive impairment.
Values are n (%) unless otherwise indicated.
[a] Weighted analyses were performed to account for the stratified random sampling that was used to select participants from visit 5 into the Atherosclerosis Risk In Communities MRI sample.

Midlife MVPA and Brain MRI Measures

Compared to participants who reported no MVPA in midlife, participants reporting high MVPA in midlife had a significantly lower odds of lacunar infarcts (odds ratio [OR] 0.68, 95% confidence interval [CI] 0.46, 0.99), and a nominally lower odds of cortical infarcts or subcortical microhemorrhages in late life (table 2). They also had greater WM microstructural integrity in late life (mean FA difference 0.13 SD [95% CI 0.004, 0.26]; mean MD difference −0.11 SD [95% CI −0.21, −0.004]). Middle levels of MVPA also indicated greater WM microstructural integrity (mean FA difference 0.23 SD [95% CI 0.06, 0.39]; mean MD difference −0.20 SD [95% CI −0.32, −0.07]). No differences in WMH burden were observed for either group. Participants reporting middle MVPA in midlife, but not those with high MVPA, had greater gray matter volumes indicated by larger AD signature region (mean difference 0.13 SD, 95% CI 0.02, 0.23) and total cortical volumes (mean difference 0.14 SD, 95% CI 0.06, 0.23) compared to participants reporting no MVPA in midlife.

We considered persistent levels of physical activity across visits 1 and 3 by categorizing participants according to persistently meeting vs persistently not meeting guidelines at both visits. Persistently meeting vs not meeting physical activity guidelines in midlife was associated with a lower odds of lacunar infarcts (OR 0.58, 95% CI 0.38, 0.90; figure 2) and larger deep gray matter volumes (mean difference 0.11 SD, 95% CI 0.003, 0.23; figure 3) in late life. Persistently meeting physical activity guidelines in midlife was not associated with cortical or subcortical microhemorrhages, significantly less WM disease, or more WM microstructural integrity.

Late-Life MVPA and Brain MRI Measures

MVPA in late life was significantly associated with most of the imaging abnormalities measured (table 3). High physical activity in late life was associated with fewer cerebrovascular lesions and less WM disease and larger gray matter volumes in late life. A lower odds of subcortical microhemorrhages (OR 0.64, 95% CI 0.45, 0.93) was observed in those participants reporting high MVPA vs no MVPA in late life. Compared to participants reporting no MVPA in late life, participants reporting high MVPA had greater WM microstructural integrity (mean FA difference 0.22 SD [95% CI 0.10, 0.34]; mean MD difference −0.17 SD [95% CI −0.26, −0.07]) and lower WMH burden (mean log [WMH volume] difference −0.23 SD, 95% CI −0.35, −0.10). They also had larger total cortical (mean difference 0.10 SD, 95% CI 0.04, 0.17) and AD signature region (mean difference 0.13 SD, 95% CI 0.05, 0.21) volumes.

Sensitivity Analyses

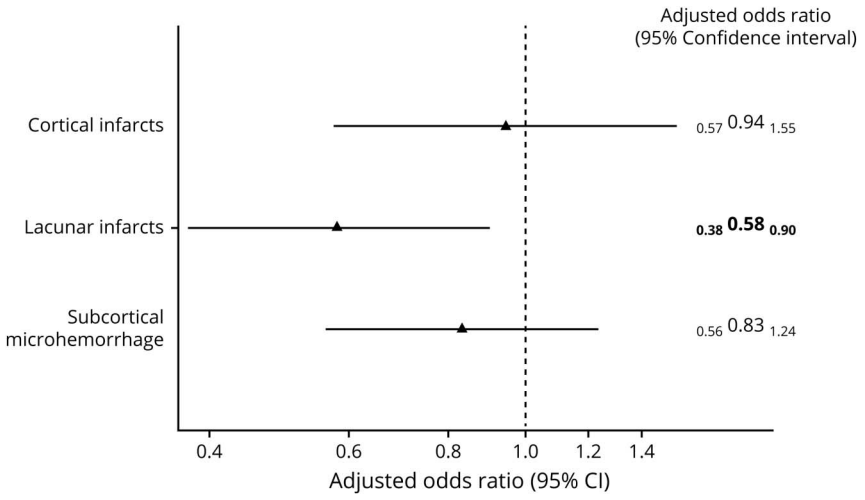
Effect estimates were attenuated and no longer reached statistical significance after adjustment for concurrent vascular

Table 2 Weighted, Adjusted Association of Midlife Leisure-Time Moderate to Vigorous Physical Activity (MVPA) With Late-Life (Visit 5: 2011–2013) Measures of Cerebrovascular Lesions, Standardized White Matter Microstructural Integrity and White Matter Disease, and Standardized Gray Matter Volumes, n = 1,604

	Min/wk of MVPA in midlife (visit 1: 1987–1989)				
	None (0 min/wk), n = 550	Low (1–74 min/wk), n = 176	Middle (75–149 min/wk), n = 250	High (≥150 min/wk), n = 628	*p*-Trend
Cerebrovascular lesions, OR (95% CI)					
Cortical infarcts	1 (Ref)	1.25 (0.65, 2.39)	0.78 (0.42, 1.47)	0.85 (0.55, 1.31)	0.314
Lacunar infarcts	1 (Ref)	0.94 (0.57, 1.55)	0.79 (0.48, 1.28)	0.68 (0.46, 0.99)	0.036
Subcortical microhemorrhage	1 (Ref)	1.30 (0.80, 2.12)	0.75 (0.46, 1.21)	0.81 (0.57, 1.16)	0.123
Per SD white matter microstructural integrity and white matter disease, β (95% CI)					
Mean fractional anisotropy[a]	0 (Ref)	0.02 (−0.16, 0.19)	0.23 (0.06, 0.39)	0.13 (0.004, 0.26)	0.021
Mean diffusivity[a]	0 (Ref)	−0.02 (−0.15, 0.12)	−0.20 (−0.32, −0.07)	−0.11 (−0.21, −0.004)	0.019
log (WMH volume)[a]	0 (Ref)	−0.06 (−0.23, 0.12)	−0.16 (−0.33, 0.02)	−0.02 (−0.14, 0.11)	0.737
Per SD gray matter volumes, β (95% CI)					
Total cortical[a]	0 (Ref)	0.005 (−0.09, 0.10)	0.14 (0.06, 0.23)	0.03 (−0.04, 0.10)	0.194
AD signature region[a]	0 (Ref)	0.007 (−0.11, 0.12)	0.13 (0.03, 0.23)	0.04 (−0.04, 0.12)	0.209
Deep gray matter[a]	0 (Ref)	0.06 (−0.08, 0.19)	0.11 (−0.01, 0.22)	0.09 (−0.01, 0.20)	0.070

Abbreviations: AD = Alzheimer disease; CI = confidence interval; OR = odds ratio; Ref = reference; WMH = white matter hyperintensity.
Adjusted for age, race–center, sex, education, *APOE* ε4, current smoking status (yes vs no), intracranial volume in volumetric analyses.
[a] 1 SD = total cortical: 42.22 cm^3; AD signature region: 6.89 cm^3; deep gray matter: 4.24 cm^3; log (WMH volume): 0.88; mean fractional anisotropy: 0.0204196; mean diffusivity: 0.0000529.

Figure 2 Weighted, Adjusted Association of Persistently Meeting vs Not Meeting 2008/2018 Physical Activity Guidelines in Midlife With Cerebrovascular Lesions in Late Life (n = 1,097)



Persistently meeting 2008/2018 physical activity guidelines in midlife, n = 391; not persistently meeting physical activity guidelines in midlife, n = 706. Persistently meeting 2008/2018 physical activity guidelines in midlife = meeting PA guidelines at both visits 1 (1987–1989) and 3 (1993–1995). Adjusted for age, sex, education, race–center, *APOE* ε4, ever smoking; bolded estimates indicate $p < 0.05$. CI = confidence interval.

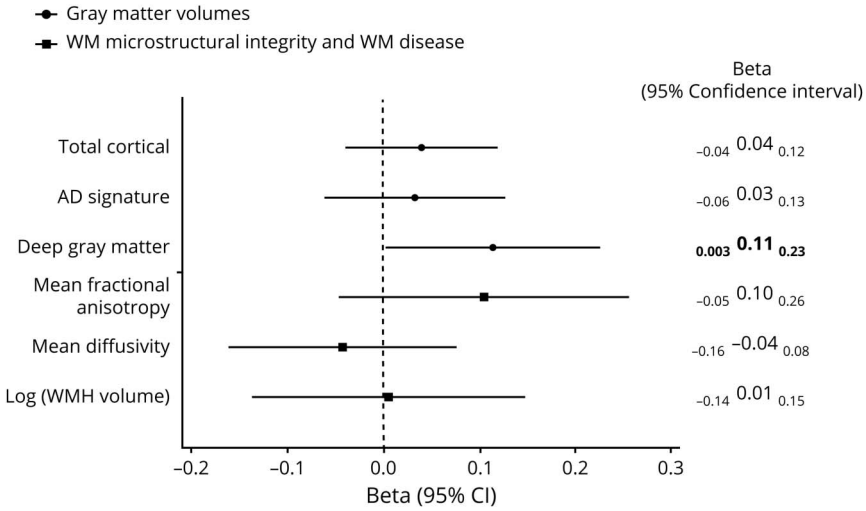
risk factors (e.g., BMI, diabetes, and hypertension) in late life (table 4). In analyses excluding clinically manifest strokes (n = 39) occurring between visits 1 and 5, effect estimates were attenuated and no longer reached nominal statistical significance for midlife measures of leisure-time MVPA with lacunar infarcts (OR 0.69, 95% CI 0.46, 1.02) and FA (mean FA difference 0.13 SD [95% CI −0.001, 0.26]).

Discussion

Consistent with our a priori hypothesis, greater physical activity levels in both midlife and late life were associated with less late-life brain damage, including fewer cerebrovascular lesions and better WM integrity. The associations of greater levels of midlife physical activity with fewer lacunar (but not cortical) infarcts and greater WM microstructural integrity suggest cerebrovascular mechanisms are primarily at play.

Our primary analysis did not adjust for vascular risk factors due to their likely part in the pathway between physical activity and the brain-related outcomes of interest, including measures of cerebral small vessel disease and neurodegeneration. Strong inverse cross-sectional associations of total daily physical activity, measured with a wrist-worn

Figure 3 Weighted, Adjusted Association of Persistently Meeting vs Not Meeting 2008/2018 Physical Activity Guidelines in Midlife With Gray Matter Volumes, White Matter (WM) Microstructural Integrity, and WM Disease in Late Life (n = 1,097)



Persistently meeting 2008/2018 physical activity guidelines in midlife (meeting 2008/2018 physical activity guidelines at both visits 1 [1987–1989] and 3 [1993–1995]), n = 391; not persistently meeting physical activity guidelines in midlife, n = 706. Adjusted for age, sex, education, race–center, *APOE* ε4, ever smoking, intracranial volume (in volumetric analyses); bolded estimate indicates $p < 0.05$. Reference: not persistently meeting physical activity 2008/2018 guidelines. 1 SD = total cortical: 42.00 cm^3; Alzheimer disease (AD) signature region: 6.85 cm^3; deep gray matter: 4.22 cm^3; log (white matter hyperintensity [WMH] volume): 0.88; mean fractional anisotropy: 0.0205635; mean diffusivity: 0.0000535. CI = confidence interval.

Table 3 Weighted, Adjusted Association of Late-Life Leisure-Time Moderate to Vigorous Physical Activity (MVPA) With Late-Life (Visit 5: 2011–2013) Measures of Cerebrovascular Lesions, Standardized White Matter Microstructural Integrity and White Matter Disease, and Standardized Gray Matter Volumes, n = 1,604

	Min/wk of MVPA in late life (visit 5: 2011–2013)				
	None (0 min/wk), n = 532	Low (1–74 min/wk), n = 110	Middle (75–149 min/wk), n = 207	High (≥150 min/wk), n = 755	*p*-Trend
Cerebrovascular lesions, OR (95% CI)					
Cortical infarcts	1 (Ref)	0.61 (0.29, 1.28)	0.76 (0.39, 1.47)	1.05 (0.65, 1.70)	0.791
Lacunar infarcts	1 (Ref)	1.38 (0.76, 2.49)	0.72 (0.44, 1.18)	0.70 (0.49, 1.01)	0.028
Subcortical microhemorrhage	1 (Ref)	1.52 (0.85, 2.71)	1.17 (0.73, 1.86)	0.64 (0.45, 0.93)	0.012
Per SD white matter microstructural integrity and white matter disease, β (95% CI)					
Mean fractional anisotropy[a]	0 (Ref)	−0.17 (−0.41, 0.08)	0.04 (−0.14, 0.21)	0.22 (0.10, 0.34)	<0.001
Mean diffusivity[a]	0 (Ref)	0.15 (−0.08, 0.39)	−0.006 (−0.15, 0.14)	−0.17 (-0.26, -0.07)	<0.001
log (WMH volume)[a]	0 (Ref)	0.17 (−0.07, 0.41)	−0.10 (−0.25, 0.06)	−0.23 (-0.35, -0.10)	<0.001
Per SD gray matter volumes, β (95% CI)					
Total cortical[a]	0 (Ref)	−0.06 (−0.16, 0.05)	0.001 (−0.09, 0.09)	0.10 (0.04, 0.17)	0.002
AD signature region[a]	0 (Ref)	−0.07 (−0.20, 0.06)	0.06 (−0.05, 0.17)	0.13 (0.05, 0.21)	<0.001
Deep gray matter[a]	0 (Ref)	−0.11 (−0.26, 0.05)	0.05 (−0.07, 0.17)	−0.02 (−0.10, 0.07)	0.920

Abbreviations: AD = Alzheimer disease; CI = confidence interval; OR = odds ratio; Ref = reference; WMH = white matter hyperintensity.
Adjusted for age, race–center, sex, education, *APOE* ε4, smoking status (ever vs never), intracranial volume in volumetric analyses.
[a] 1 SD = total cortical: 42.22 cm^3; AD signature region: 6.89 cm^3; deep gray matter: 4.24 cm^3; log (WMH volume): 0.88; mean fractional anisotropy: 0.0204196; mean diffusivity: 0.0000529.

Actical accelerometer, with postmortem imaged signs of cerebrovascular disease have been documented in a sample of 454 older adults (mean age at death 91 years, 73% female) in the Rush Memory and Aging Project.[29] Data from the Rush Memory and Aging Project also observed larger gray matter volumes with higher total levels of physical activity in 262 adults >80 years.[30] Similar findings were documented in a sample of 5,272 (mean age 55 years, 54% female) middle-aged adults from the UK Biobank Study.[31] Cross-sectional studies must be interpreted with caution due to the effects of an aging brain on behavioral changes likely to influence physical activity levels. Thus, an important and unique attribute of this study was the measurement of physical activity prospectively, decades before the assessment of brain outcomes. The association between midlife physical activity levels and later life brain imaging features makes a much stronger case for causality than does the same relationship when measured only in late life.

Few prospective studies have examined the long-term effects of physical activity on structural brain damage. Recent data from the Framingham Offspring Cohort (n = 3,714, mean age 70 years) showed that greater self-reported moderate and heavy physical activity levels measured a decade earlier and categorized in sex-specific quintiles were linearly associated with total brain and hippocampal volumes.[32] However, physical activity was measured in older adult participants, at an age where brain disease may have led to changes in physical activity behavior. Similar to ARIC, in the very small CAIDE cohort, participants (n = 75) had their leisure-time physical activity measured in midlife and again 21 years later in late life.[33] Participants who actively engaged in leisure-time physical activity in midlife had greater total brain volumes in late life compared to sedentary participants. The more active participants also had greater gray matter volumes, but showed no differences in WM volumes or lesions. Some limitations of these prior observational studies include not only the typical lack of midlife activity measurement but also the lack of repeated measures of physical activity to assess persistence in physical activity and physical activity across different life epochs. Considering the variability in physical activity over the adult life span due to changes in vigor, work, morbidity, retirement from work, and in functional abilities, a one-time measurement of physical activity may not suffice as a reliable or informative measurement of premorbid activity exposure.

We were unable to demonstrate consistent associations between midlife physical activity and brain volumetric losses, making it unlikely (though not definitively so) that physical activity directly affected upstream Alzheimer processes (amyloidosis and tauopathy). A relatively small sample of ARIC

Table 4 Weighted–Adjusted Association of Midlife Moderate to Vigorous Physical Activity (MVPA) With Late-Life (Visit 5: 2011–2013) Measures of Cerebrovascular Lesions, Standardized White Matter Microstructural Integrity and White Matter Disease, and Standardized Gray Matter Volumes, Adjusted for Vascular Risk Factors at the Time of MRI, n = 1,604

	Min/wk of MVPA in midlife (visit 1: 1987–1989)				
	None (0 min/wk), n = 550	Low (1–74 min/wk), n = 176	Middle (75–149 min/wk), n = 250	High (≥150 min/wk), n = 628	*p*-Trend
Cerebrovascular lesions, OR (95% CI)					
Cortical infarcts	1 (Ref)	1.32 (0.69, 2.55)	0.82 (0.44, 1.54)	0.89 (0.56, 1.40)	0.421
Lacunar infarcts	1 (Ref)	0.98 (0.59, 1.64)	0.83 (0.51, 1.36)	0.73 (0.50, 1.07)	0.088
Subcortical microhemorrhage	1 (Ref)	1.40 (0.86, 2.29)	0.81 (0.50, 1.33)	0.87 (0.61, 1.26)	0.247
Per SD white matter microstructural integrity and white matter disease, β (95% CI)					
Mean fractional anisotropy	0 (Ref)	0.03 (−0.14, 0.20)	0.21 (0.06, 0.37)	0.12 (−0.006, 0.25)	0.036
Mean diffusivity	0 (Ref)	0.001 (−0.14, 0.14)	−0.19 (-0.32, −0.07)	−0.09 (−0.19, 0.01)	0.038
log (WMH volume)	0 (Ref)	−0.03 (−0.20, 0.14)	−0.14 (−0.31, 0.04)	0.02 (−0.10, 0.15)	0.785
Per SD gray matter volumes, β (95% CI)					
Total cortical	0 (Ref)	−0.007 (−0.10, 0.09)	0.13 (0.05, 0.22)	0.02 (−0.05, 0.09)	0.342
AD signature region	0 (Ref)	−0.01 (−0.12, 0.10)	0.13 (0.02, 0.23)	0.03 (−0.05, 0.11)	0.313
Deep gray matter	0 (Ref)	0.04 (−0.10, 0.18)	0.11 (−0.006, 0.23)	0.09 (−0.01, 0.20)	0.071

Abbreviations: AD = Alzheimer disease; CI = confidence interval; OR = odds ratio; Ref = reference; WMH = white matter hyperintensity.
Adjusted for age, race–center, sex, education, *APOE4*, current smoking status (yes vs no), intracranial volume in volumetric analyses, hypertension, diabetes, body mass index, and stroke.
1 SD = total cortical: 42.22 cm^3; AD signature region: 6.89 cm^3; deep gray matter: 4.24 cm^3; log (WMH volume): 0.88; mean fractional anisotropy: 0.0204196; mean diffusivity: 0.0000529.

participants have undergone amyloid PET imaging[34] and tau imaging in ARIC is not currently available. Therefore information on amyloid status and Alzheimer disease risk is not available to address directly the relationship of physical activity to amyloidosis and tauopathy.

There are limitations to our study. Only self-reported LTPA measures were available, which are prone to reporting and social desirability biases,[35] and we did not include physical activity in domains other than leisure time. This supports the need for observational studies to include repeated assessments and device-based measures of physical activity into data collection protocols. Although ARIC is a biracial cohort, we chose not to conduct race-stratified analyses. The small size of ARIC's Black study population from primarily one study site limits the informativeness of race-specific analyses. Lastly, there was substantial attrition in ARIC between visits 1 and 5 (~60%), resulting in healthier participants attending the visit 5 examination and being included in this analysis. Participants with lower levels of physical activity and more brain pathology are hypothesized to be less likely to return to the visit, therefore potentially biasing our results towards the null. Several strengths should be mentioned. First, the well-characterized ARIC cohort provides over 25 years of collected data, allowing us to examine, with a prospective design, the role of persistent physical activity in midlife on structural brain damage in older adulthood. In contrast, cross-sectional analyses of physical activity with MRI-based measures of structural brain damage precludes unambiguous assignment of antecedent vs consequent elements and is potentially open to reverse causality. Furthermore, the broad range of brain findings related to late-life physical activity is likely be the result of effects of the aging brain on behavior. Therefore, our cross-temporal analysis (visit 1 exposure and visit 5 outcome) provide results whose interpretation is much clearer than those seen with physical activity at visit 5.

Our population-based findings suggest that greater levels of physical activity in midlife may protect against cerebrovascular sequelae in late life. In particular, persistently high levels of midlife physical activity were associated with fewer cerebrovascular lesions in late life, suggesting that physical activity may affect cognition largely through brain effects of small vessel disease.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Priya Palta, PhD	Columbia University Medical Center	Designed and conceptualized study, analyzed the data, has access to all the data and takes responsibility for the data, accuracy of the data analysis, and conduct of the research, interpreted the data, drafted the manuscript for intellectual content
A. Richey Sharrett, MD	Johns Hopkins University	Major role in the acquisition of data, interpreted the data, revised the manuscript for intellectual content
Kelley Pettee Gabriel, PhD	University of Alabama at Birmingham	Interpreted the data, revised the manuscript for intellectual content
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Gerardo Heiss, MD	University of North Carolina at Chapel Hill	Major role in the acquisition of data, designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content

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