

Physical activity predicts gray matter volume in late adulthood

The Cardiovascular Health Study



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ABSTRACT

Objectives: Physical activity (PA) has been hypothesized to spare gray matter volume in late adulthood, but longitudinal data testing an association has been lacking. Here we tested whether PA would be associated with greater gray matter volume after a 9-year follow-up, a threshold could be identified for the amount of walking necessary to spare gray matter volume, and greater gray matter volume associated with PA would be associated with a reduced risk for cognitive impairment 13 years after the PA evaluation.

Methods: In 299 adults (mean age 78 years) from the Cardiovascular Health Cognition Study, we examined the association between gray matter volume, PA, and cognitive impairment. Physical activity was quantified as the number of blocks walked over 1 week. High-resolution brain scans were acquired 9 years after the PA assessment on cognitively normal adults. White matter hyperintensities, ventricular grade, and other health variables at baseline were used as covariates. Clinical adjudication for cognitive impairment occurred 13 years after baseline.

Results: Walking amounts ranged from 0 to 300 blocks (mean 56.3; SD 69.7). Greater PA predicted greater volumes of frontal, occipital, entorhinal, and hippocampal regions 9 years later. Walking 72 blocks was necessary to detect increased gray matter volume but walking more than 72 blocks did not spare additional volume. Greater gray matter volume with PA reduced the risk for cognitive impairment 2-fold.

Conclusion: Greater amounts of walking are associated with greater gray matter volume, which is in turn associated with a reduced risk of cognitive impairment. *Neurology*® 2010;75:1415-1422

GLOSSARY

3MSE = modified Mini-Mental State Examination; **CHS-CS** = Cardiovascular Health Study Cognition Study; **DSST** = Digit Symbol Substitution Test; **GM** = gray matter; **MCI** = mild cognitive impairment; **OR** = odds ratio; **PA** = physical activity; **SPM** = Statistical Parametric Mapping; **TIV** = total intracranial volume; **VBM** = voxel-based morphometry; **WM** = white matter.

Gray matter (GM) volume shrinks in late adulthood, often preceding and leading to cognitive impairment.¹ Participation in physical activity (PA) and exercise, however, has been hypothesized to protect against the deterioration of brain tissue, but this hypothesis has not been tested in longitudinal studies.^{2,3} Limited support for this hypothesis comes from cross-sectional neuroimaging research demonstrating that older adults who are more fit have greater GM volume in the prefrontal and temporal lobes,⁴⁻⁶ and larger hippocampal volumes,⁷ than their less fit peers. Randomized controlled trials over 6 months have also shown increased cortical volume in response to a moderate-intensity exercise regimen.⁸

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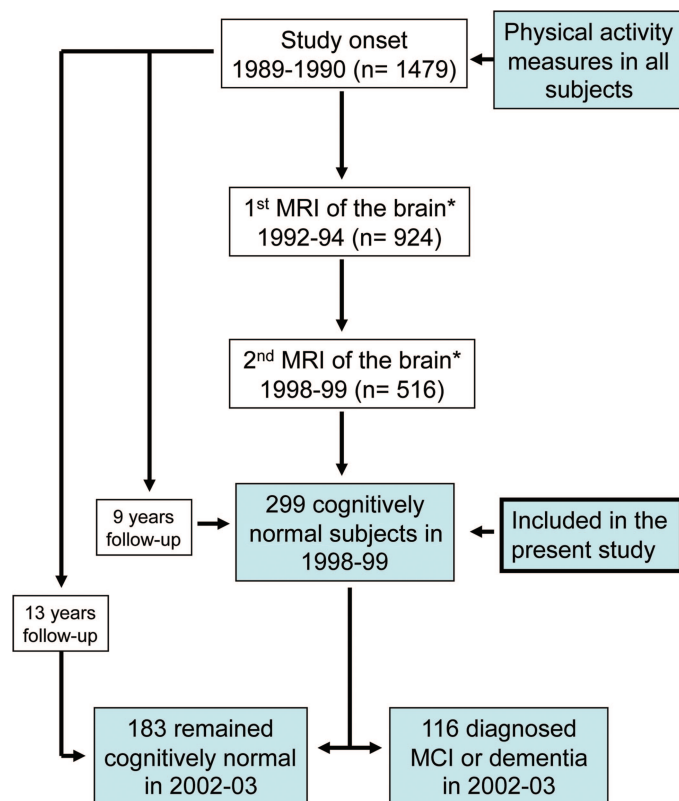
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Prospective longitudinal studies have identified physical inactivity as a risk factor for dementia,⁹⁻¹⁷ while others have found that greater PA predicts stable cognitive function over an 8-year period.¹⁸ This research suggests that participation in PA earlier in life might be predictive of less cortical shrinkage in late adulthood. Although a linear association between cognition and PA is likely, it is also possible that there is little benefit of additional PA past a certain threshold.¹⁷ Similarly, a minimal amount of PA may be necessary for any long-term protection on brain function to be detected.^{2,3,19}

In this study, we investigated whether PA, assessed at baseline, predicted GM volume 9 years later. Because brain MRI measures were unavailable at baseline and the design was not a randomized intervention, we cannot con-

clude a causal association between PA and GM volume. However, an association between PA and brain volume could be clinically meaningful. Therefore, we also predicted that greater GM volume related to PA would be associated with a reduced risk of developing cognitive impairment. In addition, we tested whether a threshold could be identified to establish a minimal amount of PA necessary to protect against the loss of GM volume and the development of cognitive impairment. We hypothesized that after controlling for several baseline measures of health and function, those participants who were more physically active would have greater GM volume at follow-up than those less active, and that greater GM volume would be associated with a reduced risk of developing cognitive impairment.

Figure 1 Subject inclusionary criteria and sample sizes



We demonstrate the longitudinal design beginning in 1989–1990 and ending with the voxel-based morphometry (VBM) analysis on high-resolution MRI data collected in 1998–1999. All participants in this sample were free of dementia and mild cognitive impairment (MCI). Originally, 1,479 individuals had physical activity assessed and 924 had a low-resolution MRI. A total of 516 of these individuals returned 5 years later for a follow-up MRI session. From these individuals, we excluded 61 with dementia, 150 with MCI, and 6 because of missing white matter grades from the first MRI assessment. Our final sample size for the VBM analysis was 299 elderly individuals between 70 and 90 years of age. *Visual rating of white matter lesions, ventricular size, atrophy, and MRI-identified infarcts.

METHODS Participants. Participants were part of the Pittsburgh component of the Cardiovascular Health Study Cognition Study (CHS-CS). The CHS-CS is derived from the larger multisite CHS, a population-based longitudinal study of coronary heart disease and stroke in individuals 65 and older. Details of the CHS design are described elsewhere.^{20,21} Participants were recruited from a Medicare database and sent a letter of invitation for participation and were enrolled if they were over 65 years of age, ambulatory, and noninstitutionalized. Baseline measures of PA were collected in 1989–1990. Low-resolution MRI were acquired 2–3 years after baseline. Acquisition of high-resolution MRI began in 1998, approximately 9 years after the baseline assessment of PA. Clinical adjudication for cognitive impairment and dementia occurred in the same year of, and 4 years after, the MRI (13 years after baseline). Detailed information about the clinical adjudication process has been previously described.²²

Characteristics of the 1,479 CHS Pittsburgh participants have been described.²⁰ Beginning in 1988–1989, participants completed the modified Mini-Mental State Examination (3MSE) and the Digit Symbol Substitution Test (DSST). From this sample, 924 met criteria (e.g., no pacemaker) for MRI. In 1998–1999, participants from the first MRI session were recruited for another MRI session. A total of 516 individuals completed this assessment. Of this number, 299 participants (mean age = 78; 182 female) met or surpassed all criteria for this study, including cognitively normal clinical status (identified by a detailed neurologic and neuropsychological assessment²²), absence of strokes or neurologic diseases (e.g., Parkinson disease) at the time of the second scan, and valid white matter (WM) hyperintensity measures from the first MRI scan (figure 1). Therefore, all participants were cognitively normal at the time of the high-resolution MRI scan. At the time of adjudication for cognitive impairment 13 years after the baseline assessment, 116 were diagnosed with dementia or mild cognitive impairment (MCI). This number is consistent with reported incidence rates for cognitive impairment.²³ For logistic regression analyses, individuals with either dementia or MCI were combined into a single group that we label here as cognitive impairment.

Standard protocol approvals, registrations, and patient consents. All participants signed an informed consent approved by the University of Pittsburgh.

Assessment of physical activity. PA was assessed at baseline by the modified Minnesota Leisure-Time Activities Questionnaire, which evaluates the duration and frequency of PA.^{24,25} The total number of blocks walked over 1 week was used as the main measure of PA. Older adults report walking more than any other type of PA (e.g., tennis), and the frequency of walking is associated with greater participation in other exercises.²⁴ Other items on the questionnaire were not used because some of them (e.g., tennis) are correlated with socioeconomic status. PA information was obtained at baseline, 9 years prior to the MRI scan.

MRI measures. Low-resolution MRI was collected 2–3 years after baseline but was too low a quality for volumetric assessment. Instead, these data were used to quantify MRI infarcts and WM grade using previously described criteria.²⁶

All high-resolution MRI data were acquired at the University of Pittsburgh Medical Center MR Research Center using a 1.5-T GE Signa scanner (GE Medical Systems, Milwaukee, WI, LX version). A 3-dimensional volumetric spoiled gradient recalled acquisition sequence was obtained for the whole brain (echo time/repetition time = 5/25, flip angle = 40°, number of excitations = 1, slice thickness = 1.5 mm/0 mm interslice gap) with an in-plane acquisition matrix of 256 × 256 × 124 image elements, 250 × 250 mm field of view, and an in-plane voxel size of 0.98 mm³.

Assessment of brain volume. Voxel-based morphometry (VBM) is a technique that estimates tissue volume in a point-by-point fashion throughout the brain. This allows regionally specific conclusions about the variables of interest on differences in brain matter. Details of the VBM approach are described elsewhere,^{27–29} but are summarized here.

We implemented an optimized VBM approach using Statistical Parametric Mapping (SPM2) software with the addition of skull-stripping and noise reduction algorithms from the FMRI Software Library. The optimized approach reduces registration error and maintains information on tissue volumes via Jacobian-based correction.^{27,28} First, brain images were smoothed with a noise reduction algorithm³⁰ and extracranial tissue was removed.³¹ Next, all images were transformed to a custom Pittsburgh Elderly Template³² with linear and nonlinear transformations. Images were then segmented into GM, WM, and CSF based on priors from the template. Voxel values were multiplied by the Jacobian determinant to calculate volume for each tissue type. The volumes of GM, WM, and CSF were summed to compute total intracranial volume (TIV). The final images were smoothed using a 10-mm (full width at half maximum) Gaussian kernel. Eigenvectors reflecting a weighted mean after controlling for the covariates (see below) were extracted from significant clusters and further analyzed in relation to cognitive impairment and dose response in the Statistical Package for Social Sciences (SPSS, v 16.0 SPSS Inc., Chicago, IL).

Statistical analysis. The relationship between walking and brain volume was assessed using the General Linear Model in SPM. Voxelwise analyses were conducted with blocks walked as a continuous variable in a multiple regression model with age, TIV, gender, body mass index, race, WM grade, MRI infarcts, ventricular grade, the time taken to walk 15 feet, and education entered as covariates of no interest. Covariates were chosen based on correlations with either PA or brain volume or because correlations between these variables were reported in prior studies.^{2–6}

Due to non-normality in the number of blocks walked, we also used log-transformed values. Values for all covariates were collected at baseline. Other potentially confounding variables such as self-report health scores, hypertension, type II diabetes, *APOE* genotype, subclinical vascular disease, and basic and incidental activities of daily living were unrelated to the number of blocks walked or GM volume, and were not included in the regression models. GM atrophy occurs with higher WM grade,³³ thus WM and ventricular grade served as a proxy for GM integrity at baseline. WM grade and the number of MRI infarcts were quantified on the low-resolution MRI using established criteria.²⁶ The time taken to walk 15 feet served to control for mobility differences. Statistical images were thresholded to ensure a false discovery rate of less than 5%.²⁸ To minimize the likelihood that any cluster of significant voxels could appear by chance, we applied a cluster threshold to ensure that at minimum, significant clusters contained at least 100 contiguous voxels.

We hypothesized that a lower-bound threshold of PA is necessary to detect differences in GM volume. To explore this, we divided the participants into quartiles based on blocks walked. This resulted in groups that walked between 0 and 12 (Q1; *n* = 91), 13 and 24 (Q2; *n* = 57), 25 and 70 (Q3; *n* = 78), and 72 and 300 blocks (Q4; *n* = 73) over a 1-week period (table 1). We then examined in an analysis of covariance whether the quartiles differed in any brain region after controlling for covariates.

Finally, in a series of logistic regression analyses adjusting for age, gender, education, race, time taken to walk 15 feet, and *APOE* allele status, we examined whether PA measured at baseline was predictive of cognitive impairment 13 years later and whether the GM volume or GM volume residuals associated with greater amounts of PA would predict cognitive impairment 4 years after the MRI assessment. Cognitive impairment was determined by clinical adjudication and included individuals with either a diagnosis of dementia or MCI.²² We report odds ratios (OR) resulting from these analyses.

RESULTS Physical activity and brain volume. The total number of blocks walked over a 1-week period ranged from 0 to 300 (mean = 56.3; median = 25; SD = 69.7). At the baseline assessment, females reported walking less than males (*r* = -0.14; *p* < 0.01). No other variables at baseline or at the time of the MRI assessment were correlated with the number of blocks walked (table 1) including hypertension, heart disease, or WM lesions. Number of blocks walked was also unrelated to the presence of cerebral infarcts, to other measures of vascular health, and to cognitive test scores at baseline. However, individuals in the highest quartile group (see below) were faster on the time to walk 15 feet test than the other 3 quartiles. The time to walk 15 feet was included as a covariate for possible mobility confounds in all analyses.

We found that walking distance assessed at baseline predicted greater volume of GM tissue 9 years later. This effect remained significant after adjusting for age, TIV, gender, WM grade, ventricular grade, MRI infarcts, the time taken to walk 15 feet, body mass index, race, and education (figure 2A). These areas included the frontal, temporal, and occipital

Table 1 Demographic and health variables^a

	Blocks walked				t Test or χ^2 , p value
	Quartile 1 (n = 91)	Quartile 2 (n = 57)	Quartile 3 (n = 78)	Quartile 4 (n = 73)	
Blocks walked, mean (SD), min/max	7.8 (4.5), 0/12	21 (3.5), 13/24	45 (13.1), 25/70	156 (75), 72/300	-14.8, <0.001 ^b
Age, y, mean (SD)	72.9 (3.7)	72.7 (3.7)	73.2 (3.6)	72.45 (3.61)	1.01, 0.31
Female (%)	66 (72.5)	29 (50.8)	51 (65.3)	35 (47.9)	6.41, 0.009 ^b
Beyond grade 12 (%)	51 (56.0)	38 (66.6)	51 (65.3)	51 (69.8)	1.66, 0.21
African American (%)	17 (18.6)	12 (21.0)	8 (10.2)	14 (19.1)	0.31, 0.59
White matter grade 3+ (%)	17 (18.6)	6 (10.5)	13 (16.6)	13 (17.8)	0.14, 0.42
MRI-identified infarcts (%)	27 (29.6)	17 (29.8)	20 (25.6)	15 (20.5)	1.71, 0.22
Heart disease (%)	9 (9.8)	12 (21.0)	15 (19.2)	12 (16.4)	0.02, 0.85
Type II diabetes mellitus (%)	15 (16.4)	4 (12.9)	6 (19.4)	6 (19.4)	0.45, 0.66
Hypertension (%)	31 (30.7)	15 (7.0)	35 (44.8)	20 (27.3)	1.76, 0.21
Time taken to walk 15 ft, s, mean (SD)	5.72 (1.72)	5.07 (1.28)	5.42 (1.79)	4.74 (1.02)	3.18, 0.002 ^b
3MSE, mean (SD)	94.71 (4.2)	95.3 (3.9)	94.8 (4.0)	94.8 (5.0)	0.18, 0.86
Digit Symbol Substitution Test, mean (SD)	48.1 (11.7)	48.5 (12.3)	48.1 (12.7)	49.0 (11.8)	-0.49, 0.63

Abbreviation: 3MSE = modified Mini-Mental State Examination.

^a Demographic, cardiovascular, and cerebral health factors measured at baseline in relation to the number of blocks walked over a 1-week period (quartiles). *p* values represent the comparison of quartile 4 with quartiles 1-3 (*df* = 297 for *t* test and *df* = 1 for χ^2 tests). Two factors were significantly related to the number of blocks: females walked less than males and the time taken to walk 15 feet was less for the highest quartile.

^b Significant.

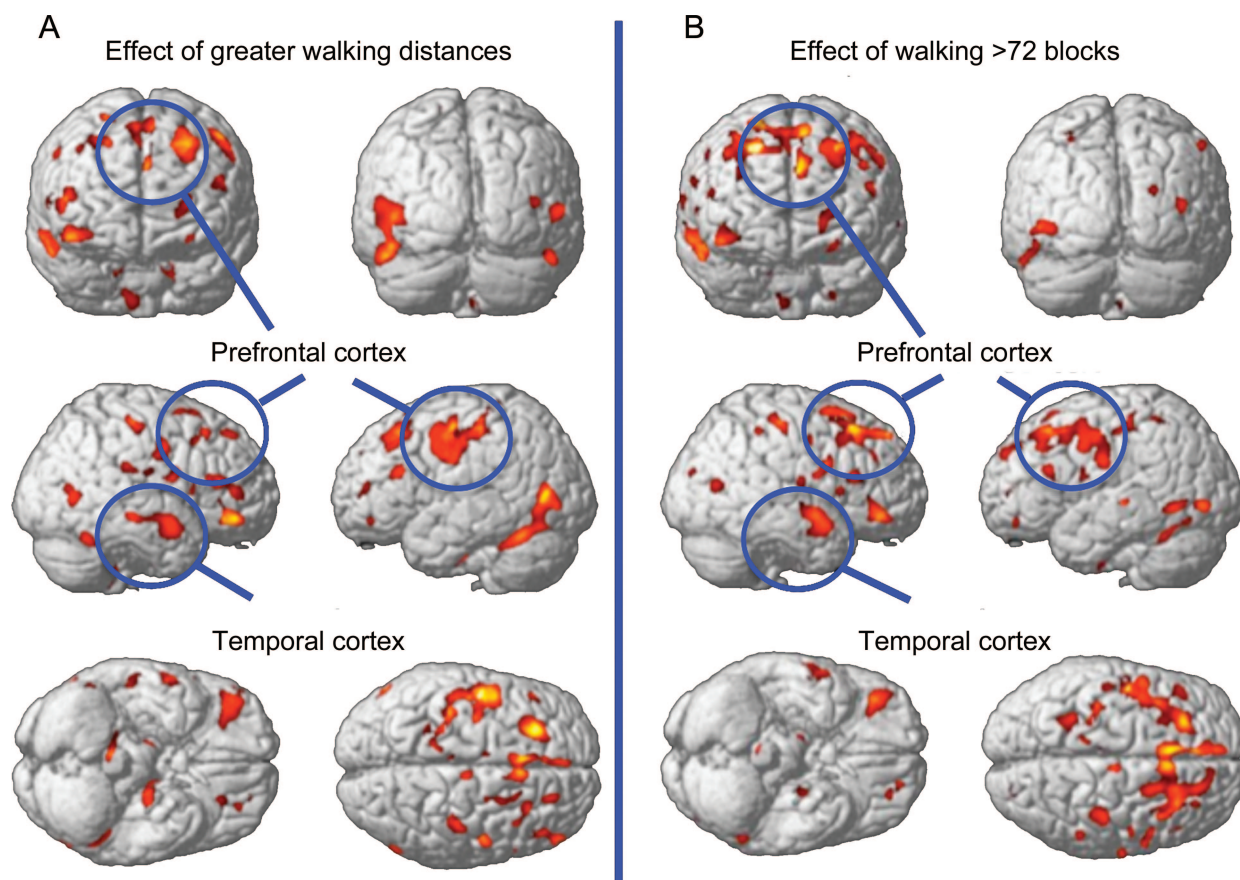
lobes (figure 2A). Both the entorhinal cortex and hippocampus were also related to walking distance with larger volumes associated with greater PA. These patterns were unchanged when using log-transformed values for the number of blocks walked. There were no regions showing greater volume with less PA and no significant interactions between blocks walked with age or gender (both *p* > 0.05).

Physical activity threshold. After splitting the participants into quartiles (Q1, Q2, Q3, Q4) based on the number of blocks walked, we found that GM volume in the highest quartile (Q4) differed from the other 3 quartiles (all *p* < 0.05; figure 2B). This effect was consistent in all brain regions that reached significance in the regression analyses reported above including the frontal cortex, the temporal lobes, and the hippocampal formation (figure 3 and table e-1 on the *Neurology*[®] Web site at www.neurology.org). There were no differences in GM volume among the lower 3 quartiles (all *p* > 0.10). Because the upper quartile was the only group that demonstrated greater GM volume than the other groups, we can assert that a large amount of PA is necessary to detect a difference in brain structure over a 9-year follow-up period.

Physical activity and risk of cognitive impairment. Of the original sample (n = 299), 116 developed MCI

(n = 64) or dementia (n = 52), while 169 remained cognitively normal (14 were deceased before the follow-up). The individuals with MCI or dementia were combined to form a single group (see Methods) and this group was used in subsequent analyses. Using logistic regression, PA was marginally related to a reduced risk of experiencing cognitive impairment 13 years later (OR = 3.20; *p* < 0.07). Measures of GM volume were not predictive of cognitive impairment (appendix e-1). However, we hypothesized that the cortical effects associated with walking greater distances would be associated with a reduced risk of developing cognitive impairment. This analysis required the use of the residual GM values from the multiple regression analysis of all covariates on GM volume. This effectively removed variance associated with the covariates and left the volume of tissue in regions that was associated with PA.

Using the adjusted GM volume values in logistic regression, we found that greater volume of the inferior frontal gyrus (OR = 1.99; *p* < 0.01), hippocampal formation (OR = 2.01; *p* < 0.009), and supplementary motor area (OR = 2.24; *p* < 0.01) were associated with a reduced risk of developing cognitive impairment. In short, walking greater distances was associated with greater GM volume in specific regions, and greater GM volume was associ-



(A) Brain regions showing an association between greater amounts of physical activity (blocks walked) at baseline and greater gray matter volume. Statistical map is thresholded with a false discovery rate of $p = 0.05$ and a minimum cluster threshold of 100 contiguous voxels. (B) Brain regions showing greater volume in the highest quartile (>72 blocks walked in 2 weeks) compared to the bottom 3 quartiles. There were no reliable differences in brain volume among the bottom 3 quartiles.

ated with a lower risk for experiencing cognitive impairment in later years.

DISCUSSION Brain tissue deteriorates in late adulthood, but greater amounts of PA have been hypothesized to spare brain tissue.^{2,3,19} In support of this hypothesis, we report that walking greater distances was associated with greater GM volume 9 years later. This effect was significant even after controlling for measures of WM lesions and MRI infarcts at baseline as well as several factors related to general health and disease such as subclinical vascular disease, ventricular grade, and hypertension. The effect was predominant in prefrontal and temporal brain regions including the hippocampus and entorhinal cortex, regions susceptible to age-related deterioration.¹

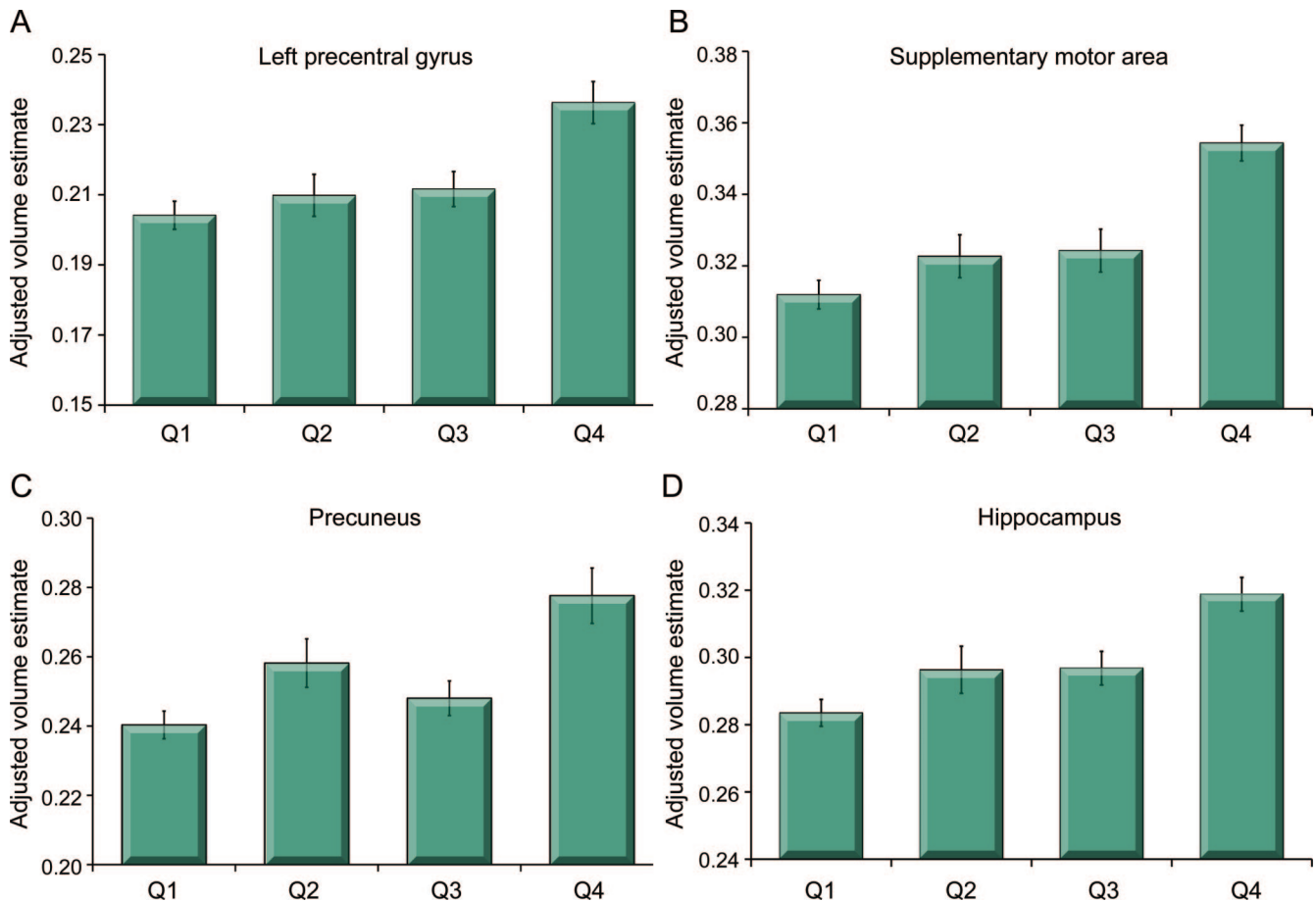
The results of this study establish 3 critical findings. First, greater amounts of PA are predictive of greater GM volume 9 years later. Second, walking relatively long distances (72 blocks or roughly 6–9 miles per week depending on the city) was necessary to detect differences in GM 9

years after the baseline evaluation of PA. Third, greater GM in the inferior frontal gyrus, the hippocampus, and the supplementary motor area was associated with a reduced risk of developing cognitive impairment (MCI or dementia).

Research in rodents provides a mechanistic explanation for the effect of exercise on brain volume and function in humans. Our results are in line with data that aerobic activity induces a host of cellular cascades that could conceivably increase GM volume. For example, running enhances learning and promotes the proliferation and survival of new neurons in the hippocampus.³⁴ The addition of new cells requires increased nutrients, which are supplied by new vasculature.³⁵ In a mouse model of AD, exercising animals show a reduction in β -amyloid deposits,³⁶ reduced tau formation,³⁷ and superior learning rates compared to sedentary animals.³⁸

Our results are encouraging, but need to be interpreted in light of some important limitations. First, we used self-reported PA. Objective assessments of PA would help in assessing the magnitude of protec-

Figure 3 Threshold effects on brain volume



Mean volumes (and SEM) of 4 brain regions (precentral gyrus [A], supplementary motor area [B], precuneus [C], and hippocampus [D]) adjusted for variance due to age, total intracranial volume, gender, body mass index, race, white matter grade, presence of MRI infarcts, and education split into quartiles based on the amount of physical activity (Q1: 0–12 blocks, $n = 91$; Q2: 13–24 blocks, $n = 57$; Q3: 25–70 blocks, $n = 78$; Q4: 72–300 blocks, $n = 73$). The highest quartile group (Q4) had greater volume in all regions examined compared with the lower 3 quartiles. No significant differences were found among the lower 3 quartiles.

tion to the brain. Second, we used only a single assessment of brain volume. Future research should examine the effect of PA on brain morphology using multiple neuroimaging time points to determine whether PA moderates the rate of GM decay. Third, given the observational nature of the study, we are unable to conclude that PA causes greater GM volume. Despite controlling for several health factors that could have explained the GM–walking relationship, there remains a possibility that reduced amounts of walking is a result of ill health and that ill health leads to both reduced amounts of walking and GM volume loss. Fourth, the results from this study are restricted to survivors over the 9-year period who were free from cognitive impairment at the time of the MRI assessment. Thus, our sample was a healthier sample than those originally enrolled in the CHS study.

Strengths include the large sample size, a well-characterized cohort followed for over 13 years, and

clinical adjudication of dementia. Based on our results, we can conclude that there is a relation between the amount of walking earlier in life and brain volume in later adulthood and that greater volume of tissue related to walking is associated with a reduced risk of cognitive impairment. Greater walking distances are associated with greater GM volume in a time period of life in which cortical deterioration and risk for dementia is greatest.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Erickson and Dr. Raji.

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DISCLOSURE

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