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RESEARCH ARTICLE

Increased sedentary behavior is associated with neurodegeneration and worse cognition in older adults over a 7-year period despite high levels of physical activity

Marissa A. Gogniat[1,2,3] | Omair A. Khan[4,5] | Judy Li[1] | Chorong Park[6] | W. Hudson Robb[1] | Panpan Zhang[1,4] | Yunyi Sun[1,4] | Elizabeth E. Moore[1,7] | Michelle L. Houston[1,8] | Kimberly R. Pechman[1] | Niranjana Shashikumar[1] | L. Taylor Davis[1,2,9] | Dandan Liu[1,4] | Bennett A. Landman[1,2,9,10,11] | Keith R. Cole[1,12] | Corey J. Bolton[1,13] | Katherine A. Gifford[1,2,14] | Timothy J. Hohman[1] | Kelsie Full[1,15] | Angela L. Jefferson[1,2,16]

[1]Vanderbilt Memory and Alzheimer's Center, Nashville, Tennessee, USA

[2]Department of Neurology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[3]Department of Neurology, University of Pittsburgh School of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

[4]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[5]Vanderbilt Brain Institute, Vanderbilt University, Medical Research Building III, Nashville, Tennessee, USA

[6]College of Nursing, Seoul National University, Jongno District, Seoul, South Korea

[7]Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts, USA

[8]Center for Biomedical Ethics and Society, Section of Surgical Sciences, Vanderbilt University Medical, Nashville, Tennessee, USA

[9]Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[10]Department of Electrical Engineering and Computer Science, Vanderbilt University, Nashville, Tennessee, USA

[11]Department of Biomedical Engineering, Vanderbilt University Center, Nashville, Tennessee, USA

[12]Department of Orthopaedic Surgery, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[13]Division of Geriatrics, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[14]Department of Anatomy and Neurobiology, Boston University, Boston, Massachusetts, USA

[15]Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[16]Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Correspondence
Angela L. Jefferson, Vanderbilt Memory and Alzheimer's Center, 3319 West End Avenue, 8th Floor, Nashville, TN 37203, USA.
Email: angela.jefferson@vumc.org

Statistical Analysis conducted by Omair A. Khan, MAS, Yunyi Sun, MA, Panpan Zhang, PhD and Dandan Liu, PhD, Department of

Abstract

INTRODUCTION: Sedentary behavior may be a modifiable risk factor for Alzheimer's disease (AD). We examined how sedentary behavior relates to longitudinal brain structure and cognitive changes in older adults.

METHODS: Vanderbilt Memory and Aging Project participants (n = 404) completed actigraphy (7 days), neuropsychological assessment, and 3T brain MRI over a 7-year period. Cross-sectional and longitudinal linear regressions examined sedentary time

Biostatistics, Vanderbilt University Medical Center

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in relation to brain structure and cognition. Models were repeated testing for effect modification by apolipoprotein E (*APOE*) ε4 status.

RESULTS: In cross-sectional models, greater sedentary time related to a smaller AD-neuroimaging signature ($\beta = -0.0001$, $p = 0.01$) and worse episodic memory ($\beta = -0.001$, $p = 0.003$). Associations differed by *APOE*-ε4 status. In longitudinal models, greater sedentary time related to faster hippocampal volume reductions ($\beta = -0.1$, $p = 0.008$) and declines in naming ($\beta = -0.001$, $p = 0.03$) and processing speed ($\beta = -0.003$, $p = 0.02$; $\beta = 0.01$, $p = 0.01$).

DISCUSSION: Results support the importance of reducing sedentary time, particularly among aging adults at genetic risk for AD.

KEYWORDS
Alzheimer's disease, brain health, cognition, sedentary

Highlights

- Greater sedentary behavior is related to neurodegeneration and worse cognition.
- Associations differed by *APOE*-ε4 carrier status in cross-sectional models.
- Sedentary behavior is an independent risk factor for Alzheimer's disease.

1 | BACKGROUND

Sedentary behavior is gaining attention as an important modifiable risk factor in aging. More time spent sitting is associated with increased risk of chronic diseases, such as type 2 diabetes, cardiovascular disease, and cancer.[1] Importantly, recent studies suggest increased sedentary time may also be associated with cognitive decline and Alzheimer's disease (AD).[2] Reducing sedentary behavior time may hold promise as an effective strategy to prevent neurodegeneration. The mechanisms underlying the detrimental effects of sedentary behavior in older adulthood are not fully understood. Prolonged sedentary time is thought to contribute to cerebral and systemic vascular dysfunction,[3] increases in inflammation,[4] and reduction in synaptic plasticity.[5] In animal models, rodents that were assigned to small cages to model a sedentary lifestyle showed higher biomarkers of oxidative stress than those who had access to a running wheel.[6] Given the association between sedentary behavior and vascular dysfunction,[7] the negative impact of sedentary behavior may be especially critical for carriers of the apolipoprotein E (*APOE*)-ε4 allele, a well-established genetic susceptibility risk factor for AD[8] and modulator of vascular damage.[9]

Regular physical activity is a well-known lifestyle strategy to maintain brain health.[10] Physical activity positively impacts brain structure, function, and cognition in older adulthood purportedly through the upregulation of neurotrophic factors[11] and synaptogenesis.[12] Physical activity intervention trials show promise for the reduction of neurodegeneration, particularly among individuals at risk for AD.[13] However, while physical activity attenuates detrimental effects of sedentary behavior, it does not completely eliminate the harmful risks associated with increased sitting time.[14] Considering the average older adult spends over 9 h sedentary during the day,[15] it is important to understand the impact of sedentary behavior on neurodegeneration and cognition in older adults, independent of physical activity.[16] Studies show older adults who engage in more sedentary behavior have worse executive function,[17] memory,[18] and neurodegeneration, particularly within the medial temporal lobe[19] and white matter.[20] In addition, a study showed that longer sedentary time measured via questionnaire was associated with higher risk of mild cognitive impairment (MCI), particularly in *APOE*-ε4 non-carriers, over a median 3-year period.[21] By contrast, a recent study did not find an association between sedentary behavior and global cognitive impairment at baseline or an association between sedentary behavior and cognitive decline over a 4 year period across several population cohorts.[22] In addition, few studies examine the independent contribution of sedentary behavior by adjusting models for other types of physical activity. These mixed results may be because prior studies vary in defining and measuring sedentary behavior (oftentimes relying upon self-report).[2,23] This heterogeneity emphasizes the need for further exploration of objectively measured sedentary behavior with comprehensive neuropsychological testing and structural brain magnetic resonance imaging (MRI), especially in a longitudinal context.

Leveraging objective measures of sedentary behavior, this study examines cross-sectional and longitudinal associations of sedentary time with cognition and structural brain changes using comprehensive neuropsychological testing in a cohort of older adults without dementia at study entry to understand risk for Alzheimer's disease and related dementias (AD). We hypothesize that, after adjustment for daily physical activity to understand the independent contribution of sedentary behavior, more sedentary time at study entry will be associated with greater neurodegeneration, particularly in brain regions susceptible to AD pathology, such as the temporal and parietal lobes.[24] We also

hypothesize that greater sedentary time at study entry will be associated with worse cognition, particularly in domains impacted by AD in the temporal lobes (i.e., memory and language), and the observed associations will be stronger for individuals genetically predisposed to AD (*APOE*-ε4 carriers vs. non carriers).

RESEARCH IN CONTEXT

1. **Systematic review**: Recent studies suggest that increased sedentary time may be associated with cognitive decline and Alzheimer's disease (AD). Reducing sedentary behavior time may hold promise as an effective strategy to prevent neurodegeneration; however, the neurobiological mechanisms underlying the detrimental effects of sedentary behavior in older adulthood are not fully understood.
2. **Interpretations**: In cross-sectional models, greater sedentary time related to cortical thinning in regions affected by AD and worse episodic memory performance. In longitudinal models, greater sedentary time also related to smaller hippocampal volume, worse naming, and processing speed. Associations differed by apolipoprotein E (*APOE*) -ε4 carrier status in cross-sectional models, driven by *APOE*-ε4 carriers.
3. **Future directions**: More sedentary time related to neurodegeneration and worse cognition cross-sectionally and longitudinally after adjustment for established AD risk and resilience factors. Results demonstrate the importance of reducing sedentary time regardless of physical activity level, particularly among aging adults at genetic risk for AD.

2 | METHODS

2.1 | Study cohort

Participants were drawn from the Legacy and Expansion Cohorts of the Vanderbilt Memory and Aging Project (VMAP), a longitudinal observational study of older adults without dementia at study entry.[25] Inclusion criteria for the Legacy Cohort required participants to be at least 60 years old with adequate auditory and visual acuity, proficiency in English, and a reliable study partner. Participants were enrolled if they were cognitively unimpaired or met existing criteria for early MCI (eMCI)[26] or MCI.[27] Inclusion criteria for the Expansion Cohort were identical except that participants had to be at least 50 years old and be cognitively unimpaired. Participants in both cohorts were excluded for MRI contraindication, a history of other neurological disorders (e.g., stroke, dementia, loss of consciousness greater than 5 min), major psychiatric illness, heart failure, or terminal illness. The present study leveraged actigraphy, neuroimaging, and neuropsychological data collected from discrete participants when actigraphy monitors were introduced in the Legacy Cohort at 18-month (2014–2016) and 3-year (2015–2018) visits. These participants were followed serially at 5-year (2017–2019), 7-year (2019–2021), 9-year (2021–2023), and 11-year (2023-ongoing) intervals. Expansion Cohort participants were asked to wear actigraphy monitors starting at study entry (2021-ongoing) and follow-up visits, including 18-month follow-up (2022-ongoing). Participants were excluded from the present study for missing covariates, actigraphy, MRI, or neuropsychological data at baseline. Of a possible 440 participants, 1 participant was excluded for missing neuroimaging data, and 35 participants were excluded for missing covariate data. Participants were included in longitudinal analyses if they had predictor and outcome data from baseline and at least one follow-up visit ($n = 244$). There were $n = 160$ participants with only one visit. This protocol was approved by the Institutional Review Board at Vanderbilt University Medical Center. Written informed consent was obtained from each participant prior to data collection. Due to participant consent restrictions in data sharing, a subset of data is available to others for purposes of reproducing the results or replicating procedures. These data, analytic methods, and study materials can be obtained by contacting the corresponding author.

2.2 | Actigraphy measures

Participants were asked to wear a triaxial accelerometer (ActiGraph GT9X Link, Actigraph, Pensacola, USA) on their non-dominant wrist 24 h per day for 10 consecutive days. The device measured acceleration in three axes at a 30 Hz sampling rate. Raw data were downloaded and exported using ActiLife software (version 6.12.1, Actigraph, Pensacola, USA) and processed in R software using the GGIR package (version 2.4-0, https://cran.r-project.org/web/packages/GGIR/).[28] GGIR auto-calibrated the data according to local gravity (*g* units; 1 $g = 9.82$ m/s^2; 1 mg = 0.00981 m/s^2), censored abnormally high accelerations, and identified non-wear time following previously validated algorithms.[29–31] Accelerations related to movement were then quantified over 5-s epochs using the Euclidian Norm Minus One (ENMO = $\sqrt{(x^2 + y^2 + z^2)}$ – 1 g), with negative values truncated to zero. Final values were expressed in m*g*.

Assessments of sedentary behavior for older adults require higher thresholds compared to younger individuals,[32] so published thresholds for wrist actigraphy variables in community-dwelling older adults were calculated as follows: (1) sedentary behavior ≤49 m*g*, (2) light physical activity (LPA) 50–99 m*g*, and (3) moderate-to-vigorous physical activity (MVPA) ≥100 mg.[33–35] Sleep periods were detected by GGIR and excluded from quantifications of sedentary behavior and physical activity.[36,37]

Excluding the first day of device wear, data from the next 7 consecutive days of wear were analyzed. A valid wear day was defined as ≥10 h of wear time.[38] Participants with fewer than 4 valid days of data were excluded.[39] Average minutes per day spent in sedentary behavior, LPA, and MVPA were calculated for each participant.

2.3 | Multi-modal 3T brain MRI and DNA genotyping

Participants underwent a brain MRI at each time point. Between 2014 and 2017, participants were scanned at the Vanderbilt University Institute of Imaging Science on a 3T Philips Achieva system (Best, the Netherlands) with an eight-channel phased-array SENSE receiver head coil. In 2017, the system was upgraded to a 32-channel dStream head coil. In the VMAP Legacy Cohort, T_1-weighted MPRAGE images were acquired using the following parameters: TR = 8.9 ms, TE = 4.6 ms, and spatial resolution = 1 × 1 × 1 mm^3. In the Expansion Cohort and VMAP Legacy Cohort from 9-year follow-up and onward, T_1-weighted MPRAGE images were acquired using the following parameters: TR = 6.5 ms, TE = 2.9ms, and spatial resolution = 1 × 1 × 1 mm^3.

T_1 images were post-processed with an established Multi-Atlas Segmentation pipeline, which calculates a consensus segmentation through fusion of anatomical labels from multiple atlases and registrations.[40,41] Regions of interest included gray matter volumes (whole brain, frontal, temporal, parietal, and occipital lobes, hippocampus). Individual gray matter, white matter, and cerebrospinal fluid volumes from T_1-weighted images were used to calculate intracranial volume (ICV). T_1-weighted images were separately post-processed using FreeSurfer version 7.3.2 (http://surfer.nmr.mgh.harvard.edu/) to obtain cortical thickness values. An AD-signature was calculated at baseline and each follow-up timepoint using FreeSurfer by summing bilateral cortical thickness measurements from regions of interest (including the entorhinal cortex, middle temporal cortex, inferior parietal cortex, fusiform gyrus, and precuneus) previously identified as susceptible to AD neurodegeneration.[42,43]

Because T_1-weighted image sequence parameters differed between the VMAP Legacy and Expansion Cohorts, we used longitudinal ComBat[44] to harmonize T_1-weighted image outputs from each segmentation pipeline across both cohorts. Longitudinal ComBat inputs include the features to be harmonized, the specification of batch variables, and the specification of a linear mixed-effects model. Input features included cortical thickness variables from Desikan-Killiany-Tourville atlas regions. Sessions were treated as independent at each timepoint.

APOE genotyping was performed on blood samples using a TaqMan single-nucleotide polymorphism (SNP) genotyping assay from Applied Biosystems (Foster City, California, USA). Polymerase chain reaction (PCR) was completed on Life Technologies 7900HT real-time PCR machine and analysis was completed using Life Technologies SDS 2.4.1 software.

2.4 | Neuropsychological assessment

Participants completed a comprehensive neuropsychological protocol at each time point assessing information processing speed, language, executive function, visuospatial ability, and episodic memory. Executive function and episodic memory composites were created using a bifactor latent variable model as previously described.[45] See Table 1 for a complete list of measures.

2.5 | Analytical plan

Linear regressions with ordinary least square estimates related average sedentary time individually to cross-sectional gray matter volumes, AD imaging signature, and neuropsychological performance (one test per model). Models were adjusted for age, sex, race/ethnicity, education (years), *APOE*-ε4 carrier status (positive, negative), Framingham Stroke Risk Profile (FSRP[46]; excluding points assigned for age), Clinical Dementia Rating (CDR) global score (0, ≥0.5) to account for cognitive status, and (as appropriate) ICV for neuroimaging outcomes. Models were repeated with the addition of MVPA as a covariate to assess the independent contribution of sedentary behavior to outcomes.

To examine associations longitudinally, linear mixed-effects regression models related baseline sedentary behavior to longitudinal neurodegeneration (gray matter volumes, AD imaging signature) and neuropsychological performance (one test per model). Identical covariates were utilized, including an interaction with time to follow-up time (in years) as the term of interest. Random intercepts and random slopes for participants were included with first-order autoregressive covariance structure to account for within participant correlations and allow participant specific trajectories.

To test for effect modification by *APOE*-ε4 status, models were repeated with a *sedentary time x APOE-ε4 status* interaction term in cross-sectional analysis and *sedentary time x APOE-ε4 status x follow-up time* interaction term in longitudinal analysis. All models were then stratified by *APOE*-ε4 status. Sensitivity analyses were performed excluding outliers in outcome variables (values > 4 standard deviations from the mean).

For additional conservative adjustment, the Benjamini-Hochberg procedure[47] was applied per hypothesis to control for false discovery rate (FDR) for multiple comparisons, and post-hoc significance was set at $p < 0.05$. Statistical analyses were conducted using R 4.2.2 (https://www.r-project.org). The following R packages were used for analyses and data visualization: dplyr (1.1.4) broom (1.0.7), Hmisc (5.2-0), ggplot2 (3.5.1), MuMIn (1.48.4), nlme (3.1-166), and rms (6.8-2).

3 | RESULTS

3.1 | Participant characteristics

Participants included 404 older adults (71 ± 9 years old, 16 ± 3 years of education, 54% male, 85% White, non-Hispanic). Most participants (79%) were cognitively unimpaired (CDR = 0) at the time of actigraphy assessment baseline. One-third of participants were *APOE*-ε4 positive ($n = 131$). Most participants met the Centers for Disease Control and Prevention (CDC) recommended guidelines of at least 150 min of MVPA per week (87%), with an average MVPA time of 61 ± 38 min per day. MVPA was strongly and inversely correlated with sedentary

TABLE 1 Baseline participant characteristics.

Parameter	Total $n = 404$	*APOE-ε4* Non-carriers $n = 273$	*APOE-ε4* Carrier $n = 131$	*p*-value
Demographic and health characteristics				
Age, years	71 ± 8.2	72 ± 8.6	70 ± 7.4	0.10
Sex, % male	54	54	55	0.83
Race, % non-Hispanic White	85	85	85	0.89
Education, years	16 ± 2.4	16 ± 2.4	16 ± 2.3	0.36
Framingham Stroke Risk Profile, total[a]	11.2 ± 4.9	11.1 ± 4.8	11.3 ± 5.0	0.94
Systolic blood pressure	135 ± 17	135 ± 16	135 ± 18	0.70
Antihypertensive medication usage, %	50	49	51	0.75
Diabetes, %	16	13	23	**0.01**
Cigarette smoking, % current	1	2	1	0.41
Prevalent CVD, %	5	4	8	0.18
Atrial fibrillation, %	6	6	5	0.83
Left ventricular hypertrophy, %	8	6	13	0.01
CDR, % 0	78	81	74	0.13
Average sedentary time, minutes/day	807 ± 97	806 ± 98	809 ± 96	0.94
Average MVPA time, minutes/day	61 ± 38	61 ± 40	60 ± 36	0.79
MVPA, % ≥150 min	87	87	88	0.78
Sleep duration, minutes/day	447 ± 81	449 ± 73	442 ± 75	0.44
Intracranial volume, mm^3	1495560 ± 147238	1489286 ± 148630	1508207 ± 144141	0.23
Brain MRI outcomes				
Total gray matter volume, mm^3	651336 ± 76297	649125 ± 77667	655777 ± 73568	0.43
Frontal lobe volume, mm^3	210642 ± 30213	209685 ± 30689	212564 ± 29258	0.35
Temporal lobe volume, mm^3	128921 ± 15417	128472 ± 15314	129823 ± 15643	0.54
Parietal lobe volume, mm^3	121650 ± 15350	121196 ± 15750	122565 ± 14527	0.30
Occipital lobe volume, mm^3	88400 ± 11075	88067 ± 11467	89071 ± 10250	0.58
Hippocampus volume, mm^3	7171 ± 801	7182 ± 784	7148 ± 837	0.74
AD-neuroimaging signature, mm	2.5 ± 0.2	2.5 ± 0.2	2.5 ± 0.2	0.73
Neuropsychological outcomes				
Boston Naming Test, total	27.5 ± 2.6	27.7 ± 2.5	27.3 ± 2.7	0.06
Animal naming, total	21.1 ± 5.8	21.3 ± 5.7	20.9 ± 6.0	0.50
WAIS-IV coding, total	56.0 ± 14	56.0 ± 14	55.0 ± 14	0.82
D-KEFS number sequencing, seconds	38.0 ± 21	37.0 ± 16	40.0 ± 21	0.16
Executive function composite	0.3 ± 0.7	0.3 ± 0.7	0.3 ± 0.8	0.89
Hooper Visual Organization Test, total	24.9 ± 2.7	25.0 ± 2.6	24.9 ± 2.8	0.70
Episodic memory composite	0.3 ± 0.9	0.4 ± 0.9	0.2 ± 0.9	0.11

Note: Values denoted as mean ± SD or frequency. Values in bold denote *p*-value < 0.05. *p*-value reflects group differences.

Abbreviations: AD, Alzheimer's disease; *APOE-ε4*, *apolipoprotein E ε4* allele; CDR, Clinical Dementia Rating; CVD, cardiovascular disease; D-KEFS, Delis–Kaplan Executive Function System; MRI, magnetic resonance imaging; MVPA, moderate to vigorous physical activity; WAIS-IV, Wechsler Adult Intelligence Scale, fourth edition.

[a]A modified Framingham Stroke Risk Profile Score was included in statistical models, which excluded points assigned to age (*APOE-ε4* carriers = 6.2 ± 3.9, *APOE-ε4* non-carrier = 5.6 ± 3.2).

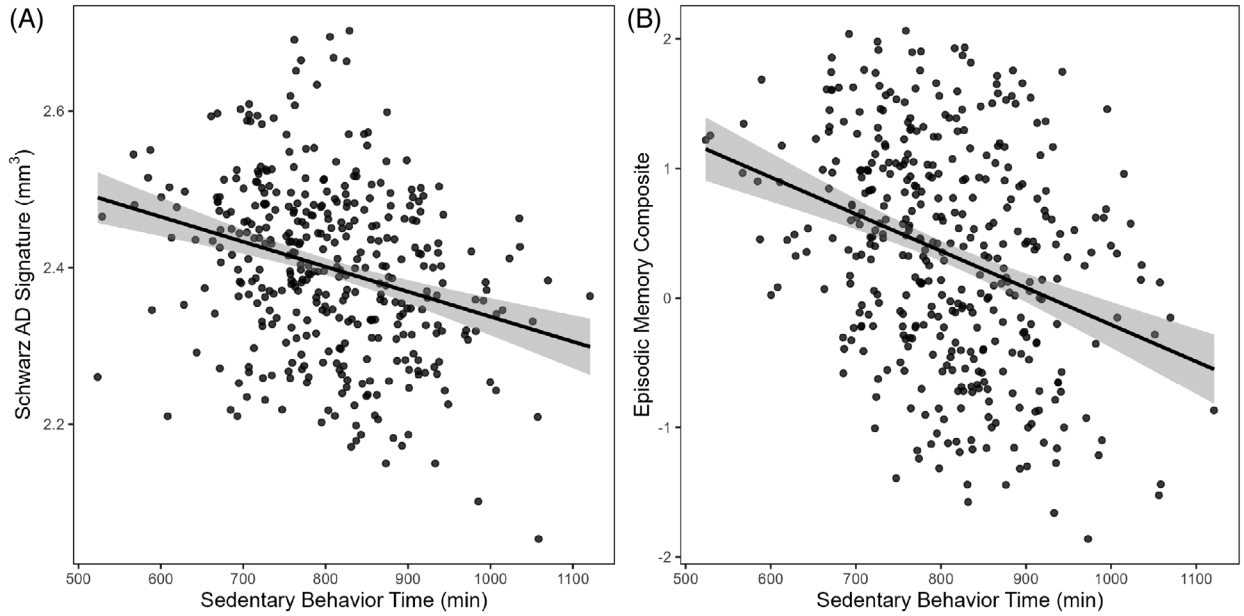

FIGURE 1 Sedentary time associations with AD-neuroimaging signature and episodic memory. Plots include outliers. For the episodic memory composite, higher values reflect better performance. Greater sedentary time was significantly associated with a smaller AD-neuroimaging signature (β = -0.0001, p = 0.01) and worse episodic memory performance (β = -0.001, p = 0.003). Models for AD-neuroimaging signature and episodic memory were attenuated when adjusting for MVPA. AD, Alzheimer's disease; MVPA, moderate-to-vigorous physical activity.

behavior (r = -0.65, $p < 0.0001$). Average sedentary time was 807 min per day (13 h). Average follow-up time was 4.7 ± 2 years. Over the course of the study, only 27 of the total participants with at least two timepoints converted to dementia. See Table 1 for additional details.

3.2 | Sedentary behavior and brain MRI outcomes

Greater sedentary time was cross-sectionally associated with a smaller AD-neuroimaging signature (β = -0.0001, p = 0.01). See Figure 1. This association remained statistically significant when excluding outliers (p-value = 0.01) but not when adjusting for MVPA (p-value = 0.07). No other cross-sectional associations were statistically significant (p-values > 0.12). See Table 2 for details and Table S1 for FDR corrected models.

The cross-sectional sedentary time x *APOE*-ε4 carrier status interacted on total gray matter (β = -86.9, p = 0.02), frontal (β = -46.9, p = 0.02), and parietal lobe volumes (β = -23.9, p = 0.02). These interactions all remained statistically significant when adjusting for MVPA (p-values = 0.02) and excluding outliers (p-values < 0.03). See Table 2 and Figure 2 for details and Table S1 for FDR corrected models. In stratified models, among *APOE*-ε4 carriers, greater sedentary time was cross-sectionally associated with lower total gray matter volume (β = -75.8, p = 0.02), and smaller frontal (β = -38.0, p = 0.02) and parietal lobe volumes (β = -18.5, p = 0.03). See Table S2 for details. All effects remained statistically significant when adjusting for MVPA except for total gray matter volume; all significant effects persisted when excluding outliers (p-values < 0.03). All stratified models in non-carriers were not statistically significant (p-values > 0.10).

In longitudinal models, greater sedentary time was associated with greater reduction in hippocampal volume over time (β = -0.1, p = 0.008). See Table 3 and Figure 3. This model remained statistically significant when adjusting for MVPA (p-value = 0.008) and excluding outliers (p-value = 0.009); see Table S3 for FDR corrected models. The sedentary time x *APOE*-ε4 carrier status interacted on occipital lobe volume annual change over time only (β = 2.0, p = 0.03). This interaction remained statistically significant when adjusting for MVPA (p-value = 0.03) and excluding outliers (p-values < 0.03). See Table 3 and Figure S1. In stratified models, among *APOE*-ε4 non-carriers, greater sedentary time was associated with greater reduction in occipital lobe volume over time (β = -1.1, p = 0.05). This effect remained significant when adjusting for MVPA (p = 0.05) and when excluding outliers (p = 0.05). All stratified models in *APOE*-ε4 carriers were not statistically significant (p-values > 0.13). See Table S4 for more details.

3.3 | Sedentary behavior and neuropsychological outcomes

Greater sedentary time was cross-sectionally associated with worse episodic memory performance (β = -0.001, p = 0.003), and the association remained statistically significant when excluding outliers (p-value = 0.03) but not when adjusting for MVPA (p-value = 0.19). See Table 2 and Figure 1 for details and Table S1 for FDR corrected models.

The cross-sectional sedentary time x *APOE*-ε4 carrier status interacted on the Boston Naming Test (β = -0.01, p = 0.01) and Hooper

TABLE 2 Sedentary time cross-sectional associations with brain health and cognition.

Parameter	β Sedentary time	95% CI	p-value	p-value with MVPA
Brain MRI outcomes				
Total gray matter volume	−25.4	−63.1, 12.3	0.19	0.14
Frontal lobe volume	−9.1	−28.7, 10.5	0.36	0.17
Temporal lobe volume	−1.8	−10.5, 6.8	0.68	0.65
Parietal lobe volume	−5.0	−14.9, 4.9	0.32	0.35
Occipital lobe volume	−4.9	−11.1, 1.3	0.12	0.15
Hippocampus volume	−0.2	−1.0, 0.5	0.52	0.97
AD-neuroimaging signature	−0.0001	−0.0002, −0.00003	**0.01**	0.07
Neuropsychological outcomes				
Boston Naming Test	0.0002	−0.002, 0.003	0.89	0.69
Animal naming	−0.006	−0.01, −0.0005	**0.03**	0.37
WAIS-IV coding	−0.001	−0.01, 0.01	0.93	0.38
D-KEFS number sequencing[a]	−0.003	−0.02, 0.01	0.69	0.09
Executive function composite	−0.0002	−0.001, 0.0004	0.47	0.43
Hooper Visual Organization Test	−0.001	−0.004, 0.002	0.42	0.97
Episodic memory composite	−0.001	−0.002, -0.0004	**0.003**	0.19
Sedentary time x *APOE*-ε4 on brain MRI outcomes				
Total gray matter volume	−86.9	−160.9, -13.0	**0.02**	**0.02**
Frontal lobe volume	−46.9	−85.3, -8.5	**0.02**	**0.02**
Temporal lobe volume	−7.8	−24.9, 9.3	0.37	0.37
Parietal lobe volume	−23.9	−43.4, -4.5	**0.02**	**0.02**
Occipital lobe volume	3.0	−9.3, 15.3	0.63	0.62
Hippocampus volume	−0.6	−2.0, 0.9	0.44	0.43
AD-neuroimaging signature	−0.0002	−0.0004, 0.00003	0.09	0.08
Sedentary time x *APOE*-ε4 on neuropsychological outcomes				
Boston Naming Test	−0.01	−0.01, -0.001	**0.01**	**0.01**
Animal naming	−0.003	−0.01, 0.007	0.55	0.52
WAIS-IV coding	−0.003	−0.03, 0.02	0.83	0.80
D-KEFS number sequencing[a]	0.02	−0.02, 0.05	0.31	0.28
Executive function composite	−0.001	−0.002, 0.0003	0.14	0.12
Hooper Visual Organization Test	−0.007	−0.01, -0.001	**0.01**	**0.01**
Episodic memory composite	−0.0002	−0.001, 0.001	0.77	0.73

Note: Values in bold denote *p*-value < 0.05.

Abbreviations: AD, Alzheimer's disease; *APOE*-ε4, apolipoprotein E ε4; CI, confidence interval; D-KEFS, Delis-Kaplan Executive Function System; MRI, magnetic resonance imaging; MVPA, moderate-to-vigorous activity; WAIS-IV, Wechsler Adult Intelligence Scale, fourth edition.

[a]Higher values reflect worse performance.

Visual Organization Test performance (β = -0.01, p = 0.01). See Table 2 and Figure 2. These effects remained statistically significant when adjusting for MVPA (p-values = 0.01) and excluding outliers (p-values < 0.02). When these significant models were stratified by *APOE*-ε4 status, sedentary time related to the Hooper Visual Organization Test in *APOE*-ε4 carriers only (β = -0.01, p = 0.03). This effect remained statistically significant when excluding outliers (p = 0.009) but not when adjusting for MVPA (p = 0.32). See Table 2 and Table S2 for more details.

In longitudinal models, greater sedentary time was associated with greater decline in naming (β = -0.001, p = 0.03), Wechsler Adult Intelligence Scale - fourth edition (WAIS-IV) Coding, (β = -0.003, p = 0.02) and Delis–Kaplan Executive Function System (D-KEFS) Number Sequencing speed (β = 0.01, p = 0.01) over time. See Table 3, Figure 3, and Table S3 for FDR corrected models. These associations remained statistically significant when also adjusting for MVPA (p-values < 0.03). When excluding outliers, all observed associations persisted (p-values < 0.04) except for naming (p-value > 0.13). No longitudinal interactions

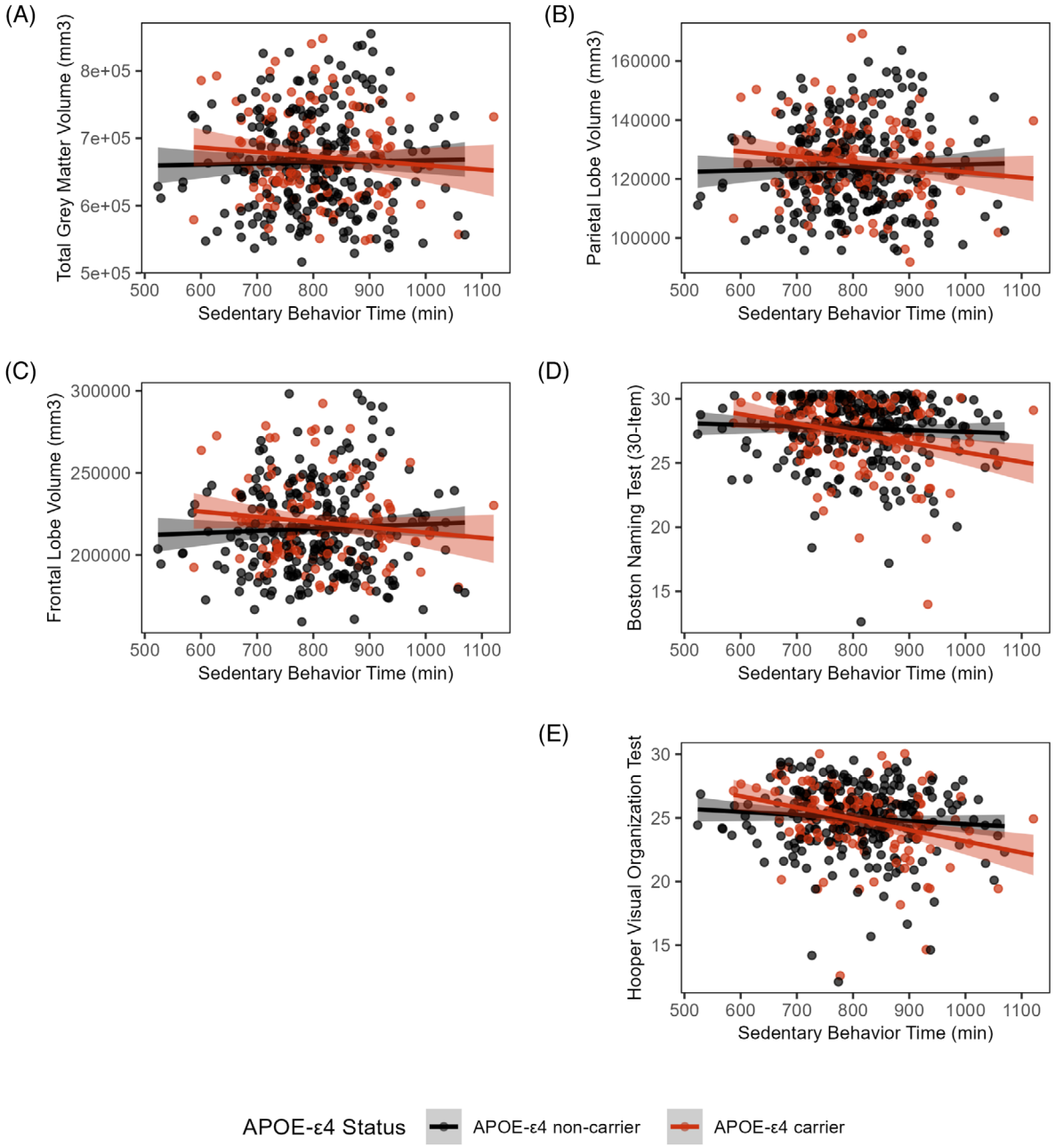

FIGURE 2 Cross-sectional sedentary time x *APOE*-ε4 on neurodegeneration and cognition. Plots include outliers. Sedentary time interacted with *APOE*-ε4 carrier status on (A) total gray matter ($\beta = -86.9$, $p = 0.02$), (B) parietal lobe ($\beta = -23.9$, $p = 0.02$), and (C) frontal lobe ($\beta = -46.9$, $p = 0.02$) volumes. Models remained significant when adjusting for MVPA. Sedentary behavior time x *APOE*-ε4 carrier status interacted on (D) Boston Naming Test performance ($\beta = -0.01$, $p = 0.01$) and (E) Hooper Visual Organization Test performance ($\beta = -0.01$, $p = 0.01$). All plots include outliers. Models remained significant when adjusting for MVPA. *APOE*, apolipoprotein E; MVPA, moderate-to-vigorous physical activity.

by *APOE*-ε4 carrier status were observed (*p*-values > 0.08; see Table 3).

4 | DISCUSSION

In a cohort of community-dwelling older adults free of dementia at study baseline, we examined how objectively measured sedentary behavior related to measures of neurodegeneration and cognition cross-sectionally and over a 7-year (mean 4.7) follow-up period. We found that greater sedentary behavior was cross-sectionally associated with a smaller AD-neuroimaging signature of cortical thickness and worse episodic memory performance. Longitudinally, greater sedentary time at baseline was associated with faster hippocampal atrophy and faster decline in naming and information processing speed performance. Many of the observed associations cross-sectionally linking sedentary time with structural neuroimaging and cognitive outcomes were present in *APOE*-ε4 carriers but not non-

TABLE 3 Sedentary time associations with longitudinal brain health and cognition.

Parameter	B Sedentary time	95% CI	*p*-value	*p*-value with MVPA
Brain MRI outcomes				
Total gray matter volume	−3.7	−13.5, 6.2	0.47	0.47
Frontal lobe volume	−2.0	−6.8, 2.9	0.42	0.42
Temporal lobe volume	−0.4	−2.0, 1.3	0.66	0.66
Parietal lobe volume	−0.7	−3.1, 1.8	0.60	0.60
Occipital lobe volume	−0.4	−1.3, 0.6	0.45	0.45
Hippocampus volume	−0.1	−0.2, -0.04	**0.008**	**0.008**
AD-Neuroimaging Signature	−0.00001	−0.00003, 0.00001	0.22	0.22
Neuropsychological outcomes				
Boston Naming Test	−0.001	−0.001, -0.0001	**0.03**	**0.03**
Animal naming	−0.001	−0.002, 0.0001	0.07	0.06
WAIS-IV coding	−0.003	−0.01, -0.0004	**0.03**	**0.02**
D-KEFS number sequencing[a]	0.01	0.002, 0.01	**0.007**	**0.007**
Executive function composite	−0.0002	−0.0003, 0.00001	0.06	0.06
Hooper Visual Organization Test	−0.0001	−0.001, 0.001	0.84	0.83
Episodic memory composite	−0.0001	−0.0002, 0.00003	0.11	0.10
Sedentary time x *APOE*-ε4 on brain MRI outcomes				
Total gray matter volume	11.5	−7.3, 30.3	0.23	0.22
Frontal lobe volume	4.7	−4.4, 13.7	0.31	0.30
Temporal lobe volume	−0.7	−0.7, 6.1	0.11	0.11
Parietal lobe volume	2.8	−2.0, 7.5	0.25	0.25
Occipital lobe volume	2.0	0.2, 3.8	**0.03**	**0.03**
Hippocampus volume	−0.01	−0.2, 0.2	0.93	0.92
AD-Neuroimaging Signature	−0.00001	−0.00004, 0.00003	0.67	0.77
Sedentary time x *APOE*-ε4 on neuropsychological outcomes				
Boston Naming Test	0.001	−0.0001, 0.002	0.08	0.08
Animal naming	−0.001	−0.003, 0.002	0.65	0.65
WAIS-IV coding	0.001	−0.004, 0.006	0.65	0.65
D-KEFS number sequencing[a]	0.01	−0.001, 0.03	0.07	0.07
Executive function composite	0.00002	−0.0004, 0.0004	0.93	0.92
Hooper Visual Organization Test	−0.0003	−0.002, 0.001	0.59	0.59
Episodic memory composite	−0.0002	−0.001, 0.0001	0.22	0.22
Boston naming test	0.001	−0.0001, 0.002	0.08	0.08

Note: Values in bold denote *p*-value < 0.05.
Abbreviations: AD, Alzheimer's disease; *APOE*-ε4, apolipoprotein E ε4; CI, confidence Interval; D-KEFS, Delis-Kaplan Executive Function System; MRI, magnetic resonance imaging; MVPA, moderate-to-vigorous activity; WAIS-IV, Wechsler Adult Intelligence Scale, fourth edition.
[a]Higher values reflect worse performance.

carriers. These associations persisted in interactions models only cross-sectionally and in main effects models and interaction models longitudinally after statistical adjustment for MVPA, providing a much better understanding of how sedentary behavior may contribute to neurodegeneration and cognitive changes in aging independently of physical activity, especially among individuals at greater genetic risk for sporadic AD.

More sedentary time was related to a smaller AD-neuroimaging marker of cortical thickness and worse episodic memory cross-sectionally, which is supported by previous literature.[15,18,23] Taken together, these results support that a higher amount of sedentary behavior is related to both AD-related neurodegeneration and AD-related cognitive changes, suggesting a common mechanism of action. Given the associations between sedentary behavior and increased

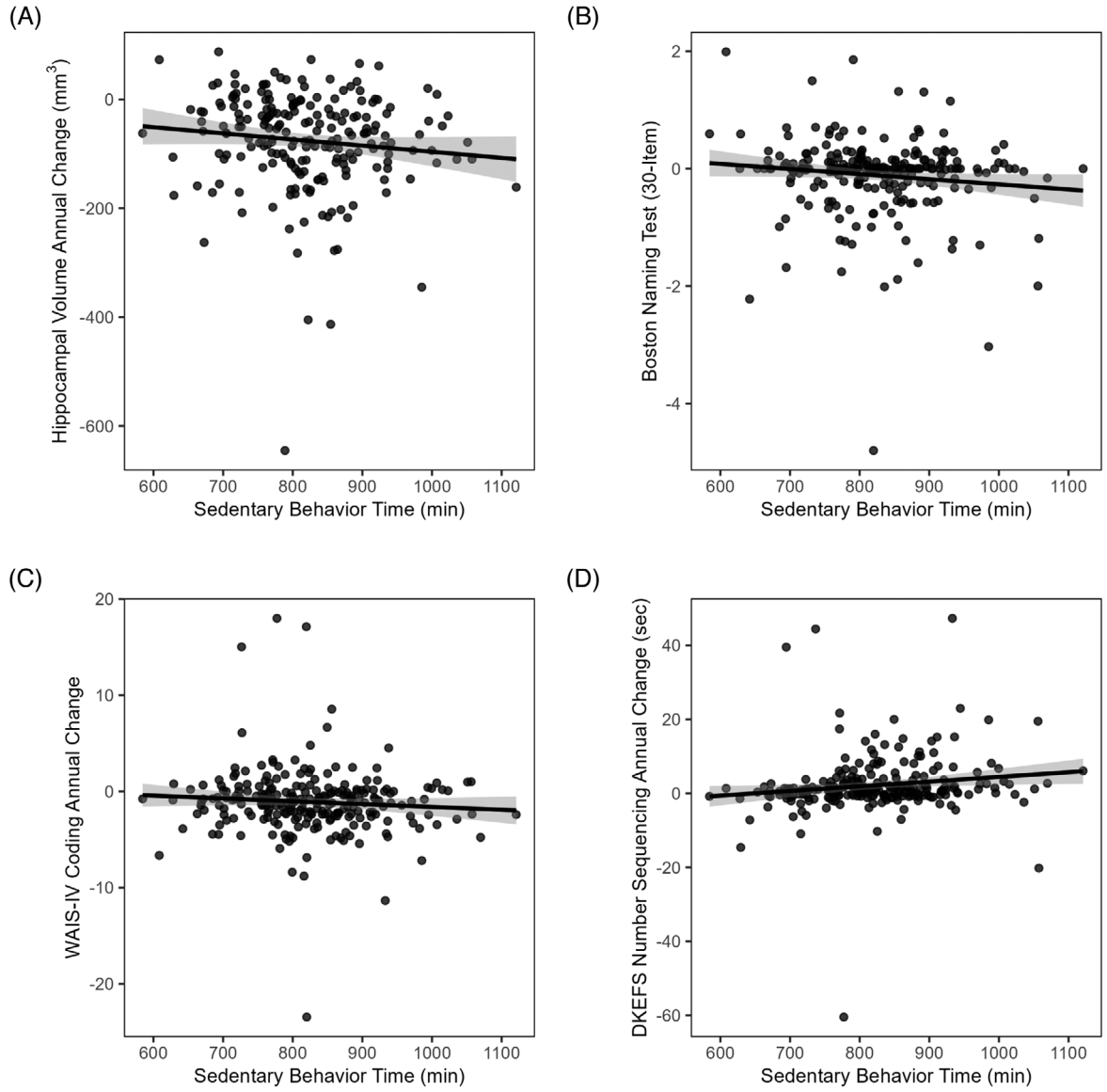

FIGURE 3 Sedentary time associations with longitudinal neurodegeneration and cognition. Plots include outliers. For naming and WAIS-IV, higher values reflect better performance. Greater sedentary time related to smaller hippocampal volume ($\beta = -0.1$, $p = 0.008$), and worse naming ($\beta = -0.001$, $p = 0.03$), WAIS-IV Coding ($\beta = -0.003$, $p = 0.02$), and D-KEFS Number Sequencing ($\beta = 0.01$, $p = 0.01$) speed. Models remained significant when adjusting for MVPA. D-KEFS, Delis–Kaplan Executive Function System; MVPA, moderate-to-vigorous physical activity; WAIS-IV, Wechsler Adult Intelligence Scale - fourth edition.

cerebrovascular dysfunction,[7] this may be one mechanism by which sedentary behavior increases the risk for structural brain and cognitive changes. It is important to note that these results were the only results to be attenuated after statistical adjustment for MVPA, suggesting that level of MVPA may play an important role in cross-sectional associations linking sedentary behavior to brain health and sedentary behavior to cognition.

Notably, associations between greater sedentary behavior, neurodegeneration, and worse cognition typically persisted, especially when taking into account MVPA longitudinally, with 87% of the sample accomplishing the amount and intensity of weekly physical activity recommended by the CDC.[48] This finding suggests that mechanisms underlying the negative impacts of greater sedentary behavior may be operating independently of the mechanisms underlying the positive impacts of physical activity, and perhaps physical activity does not mitigate all the harmful effects of being sedentary. This finding is in line with other studies suggesting the independent and adverse impact of increased sedentary behavior on health outcomes.[2,16] Future work should consider sedentary behavior and physical activity as interrelated but independent constructs.

Results also indicated that cross-sectional associations varied by *APOE-ε4* status in several brain regions (total gray matter volume; frontal and parietal lobe volumes), which extends prior literature suggesting that just the medial temporal lobe is susceptible to the deleterious effects of increased sedentary behavior.[19] Importantly, observed results persisted when adjusting for MVPA and survived

correction for multiple comparisons, highlighting a robust and independent contribution of greater sedentary behavior to global neurodegeneration based on *APOE*-ε4 carrier status. Sedentary behavior also interacted cross-sectionally with *APOE*-ε4 status on cognition, including language and visuospatial performances. These results persisted when adjusting for MVPA, again, suggesting a robust and independent contribution of sedentary behavior. Stratified results by *APOE*-ε4 status were significant for visuospatial performance in *APOE*-ε4 carriers only. Future studies should continue to investigate these relationships in the context of genetic risk factors. Taken together with the *APOE*-ε4 interactions on brain MRI outcomes, *APOE*-ε4 carriers appear to be at increased risk for neurodegeneration associated with greater sedentary behavior, independent of physical activity level.

Longitudinal results showed that greater sedentary behavior was associated with structural brain and cognitive changes associated with AD over an average follow-up of 4.7 years. While these results align with previous cross-sectional work,[19,20] longitudinal data have been sparse, with one study finding no association between greater sedentary behavior and brain volume over time in middle-aged adults.[49] Another study found that sedentary time was not associated with cognition over time but the study focused exclusively on global cognition[50] rather than individual cognitive domains as was analyzed here. To our knowledge, our study is among the first to demonstrate that greater sedentary behavior is longitudinally associated with smaller hippocampal volume and worse cognitive performance. These findings suggest that above and beyond physical activity level, more sedentary behavior is still worse for brain health and cognition over time in areas that correspond with AD-specific changes, suggesting a shared mechanism. These results complement and extend our cross-sectional results. Interestingly, we only found a sedentary time x *APOE*-ε4 status interaction on occipital volume longitudinally (which did not survive correction for multiple comparisons) and no interactions on cognition. The significant effect on occipital lobe volume was driven by *APOE*-ε4 non-carriers, which does not align with our cross-sectional findings. *APOE*-ε4 carriers are thought to have accelerated gray matter volume loss, starting possibly in middle age.[51] Therefore, while increased sedentary time may impact gray matter volume among *APOE*-ε4 carriers, this effect may be masked by the cumulative effect of *APOE*-ε4 on brain volume over the lifespan that is captured at baseline. Given the mean age of our participants at baseline was 71 years, future work may benefit from following participants over a longer timespan that starts earlier in middle age.

This study has several notable strengths including a large, well-characterized community cohort with neuroimaging, objectively measured daily activity over one week, and a comprehensive neuropsychological protocol. However, there are some important limitations. First, the sample lacked racial and ethnic diversity and was well educated, limiting the generalizability of results to the general population of older adults. In addition, our sample was quite active while wearing the actigraphy devices with 87% of participants meeting the CDC recommendation of at least 150 min of MVPA per week.[48] While such an active sample may limit generalizability, it provides strong evidence that even among a physically active cohort, such increased activity is not protective from the impact of greater sedentary behavior and brain health, especially among *APOE*-ε4 carriers. Some methodological limitations of our study are that we utilized cross-sectional MRI registration at each time point versus longitudinal registration, and the AD neuroimaging signature we used may not capture atypical presentations of AD-related neurodegeneration.[52] Another methodological limitation is using some individual neuropsychological subtests instead of composites, which limits power but may improve specificity. Additionally, it might be important to consider the 24-h activity period in future analyses. While there were no differences in results when including sleep duration as a covariate (results not shown), a compositional analysis that considers movement throughout the 24-h cycle may answer questions about the optimal allocation of physical activity, sedentary behavior, and sleep. Finally, while using objectively measured activity is a strength of this study, the position of the actigraphy device may affect the accuracy of activity measurements,[53] so our findings with wrist actigraphy may differ from other studies using a thigh or waist device placement.

In conclusion, we found that greater sedentary behavior was associated with worse neurodegeneration and cognition cross-sectionally and longitudinally despite high levels of physical activity among the cohort. These findings are particularly important in the context of aging, as mobility limitations and greater sedentary time increases in older adults. This study also contributes novel and preliminary information to our understanding of how sedentary behavior may interact with genetic risk for AD. From a personalized medicine approach, healthcare professionals might consider assessing not only a patient's exercise regimen but also the amount of time they are sedentary throughout the day, recommending a reduction in such sedentary behavior in addition to increasing daily physical activity. In summary, this study contributes to our understanding of how greater sedentary behavior is associated with AD-related neurodegeneration and cognition changes. Future work may consider exploring the underlying biological mechanisms that contribute to these associations, which could inform treatment and prevention efforts.

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CONFLICT OF INTEREST STATEMENT

T.J.H. serves on the Scientific Advisory Board for Vivid Genomics. T.J.H. is also Deputy Editor for Alzheimer's & Dementia: Translational Research and Clinical Intervention and Senior Associate Editor

for Alzheimer's & Dementia. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided informed consent.

ORCID

Marissa A. Gogniat https://orcid.org/0000-0001-8331-693X

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SUPPORTING INFORMATION

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