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RESEARCH ARTICLE

Longitudinal associations between exercise and biomarkers in autosomal dominant Alzheimer's disease

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Abstract

INTRODUCTION: We investigated longitudinal associations between self-reported exercise and Alzheimer's disease (AD)-related biomarkers in individuals with autosomal dominant AD (ADAD) mutations.

METHODS: Participants were 308 ADAD mutation carriers aged 39.7 ± 10.8 years from the Dominantly Inherited Alzheimer's Network. Weekly exercise volume was measured via questionnaire and associations with brain volume (magnetic resonance imaging), cerebrospinal fluid biomarkers, and brain amyloid beta (Aβ) measured by positron emission tomography were investigated.

RESULTS: Greater volume of weekly exercise at baseline was associated with slower accumulation of brain Aβ at preclinical disease stages $\beta = -0.16$ [−0.23 to −0.08], and a slower decline in multiple brain regions including hippocampal volume $\beta = 0.06$ [0.03 to 0.08].

DISCUSSION: Exercise is associated with more favorable profiles of AD-related biomarkers in individuals with ADAD mutations. Exercise may have therapeutic potential for delaying the onset of AD; however, randomized controlled trials are vital to determine a causal relationship before a clinical recommendation of exercise is implemented.

KEYWORDS
Alzheimer's disease, exercise, magnetic resonance imaging, positron emission tomography, physical activity

Highlights

- Greater self-reported weekly exercise predicts slower declines in brain volume in autosomal dominant Alzheimer's disease (ADAD).
- Greater self-reported weekly exercise predicts slower accumulation of brain amyloid beta in ADAD.
- Associations varied depending on closeness to estimated symptom onset.

1 | BACKGROUND

Physical inactivity is an important modifiable risk factor for Alzheimer's disease (AD).[1] Greater physical activity is associated with reduced risk for all-cause dementia and AD,[2–5] better cognition,[6,7] and greater brain volume in AD-susceptible regions.[8–11] Physical activity is also associated with more favorable AD-related biomarker profiles, including amyloid beta (Aβ) and tau, in the blood, cerebrospinal fluid (CSF), and brain.[12,13] Exercise (a structured or planned form of physical activity) is associated with better cognition across the AD trajectory.[14,15] However, it is currently unclear at which disease stage exercise is associated with the greatest benefit for AD-related outcomes, and whether such benefits are sustained across the disease course.

Autosomal dominant AD (ADAD) is a rare form of AD attributable to mutations on either the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*) genes.[16] Individuals with ADAD provide a unique opportunity to draw temporal conclusions about the disease course because they are destined to develop AD at a mutation-specific age, meaning it is possible to examine at which disease stages intervention implementation might be most effective. Further, because individuals with ADAD are younger at disease onset, they are likely free of many age-related comorbidities which make interpretation of the association between exercise and AD-related biomarkers challenging in older adults.

Previous cross-sectional studies have suggested that in individuals with ADAD, greater self-reported exercise duration ($\geq$ 150 minutes/week) was associated with better cognition at the expected age of symptom onset, lower levels of AD-related biomarkers in CSF, and in those already accumulating brain Aβ (i.e., Aβ positive), lower brain Aβ levels.[17,18] However, to our knowledge, no studies have considered longitudinal associations between exercise and AD biomarkers in individuals with ADAD, and such research will help further our understanding of the potential of exercise as a therapeutic strategy to delay the onset of AD.

The current study used data from the Dominantly Inherited Alzheimer Network (DIAN), a multi-site, international observational study of individuals from families who carry ADAD mutations. Our primary aim was to examine associations between self-reported exercise and AD-related markers (CSF biomarkers, brain Aβ, and brain structure) over time, and determine whether associations varied depending on closeness to estimated years from expected symptom onset (EYO). We therefore considered the following research questions: (1) are baseline and longitudinal self-reported exercise levels associated with AD-related markers over time? and (2) do baseline and longitudinal associations between self-reported exercise and AD biomarkers differ depending on estimated years from expected symptom onset?

2 | METHOD

2.1 | Participants

From DIAN data freeze 14 (data collected from January 2009 to June 2019), there were a total of 534 participants with available data; after removing Dutch mutation carriers (*APP* E693Q mutation that causes cerebral amyloid angiopathy), mutation non-carriers, outliers (defined below), and those with missing self-reported exercise data, there remained 308 participants (see Figure 1). In the DIAN study the visit schedule for follow-up assessments varies based on how close a participant is to their estimated year of symptom onset, with 3-year intervals for asymptomatic individuals and 1-year intervals for individuals within 3 years of the parent's age at onset.[19] Participants were included if they had data for $\geq$ 1 of our outcome variables of interest; thus, sample size varied depending on the outcome variable and ranged from n = 254 for brain Aβ to n = 307 for CSF (Figure 1). All assessment and imaging procedures for the DIAN study were approved by the Washington University Human Research Protection Office. Written informed consent was obtained from all individuals or their caregivers.

2.2 | Estimated years from symptom onset

The age at onset (AAO) for ADAD cognitive symptoms can be estimated based on parental AAO (the first progressive change in cognition or behavior of the parent) or mean mutation AAO (used if available;[20] otherwise, parental onset age is used). Thus, the disease stage can be

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional database searches. Previous studies have examined the association between physical activity and Alzheimer's disease (AD) biomarkers; however, only two previous cross-sectional studies have examined this association in individuals with autosomal dominant AD mutations.
2. **Interpretation**: Our findings demonstrate that greater weekly exercise is associated with slower accumulation of brain amyloid beta and slower decline in brain volume in individuals who are destined to develop AD.
3. **Future directions**: Exercise may have therapeutic potential for delaying the onset of AD; however, randomized controlled trials are vital to determine a causal relationship before a clinical recommendation of exercise is implemented. These associations should be further studied in individuals with late-onset AD.

projected based on how far away an individual is from their EYO.[21] If parental AAO is used, this is determined after careful discussion with a reliable collateral source, the participant, and any other sources of information that are useful for determination (e.g., medical records, other family members). EYO is calculated by subtracting the estimated AAO (from mutation data or parental age of onset) from the participant's age at the time of assessment, resulting in negative values indicating years until estimated conversion, and positive values indicating years since expected symptom onset. Efforts were made to account for differences between estimated and actual symptom onset, resulting in the removal of two individuals who remained cognitively normal (Clinical Dementia Rating [CDR] = 0) ≥ 12 years post EYO (Figure 1).

2.3 | Exercise level evaluation

At baseline and each subsequent follow-up visit, participants self-reported their average minutes per week spent partaking in 10 leisure-time exercise activities (e.g., walking, jogging, cycling, swimming, tennis, aerobics, yoga, and weight training) over the past 12 months. In the questionnaire instructions, participants were encouraged to have their responses corroborated by their collateral source (e.g., family member or friend). Research from our group has previously shown internal consistency for this questionnaire.[17] Consistent with our previous work, individual item responses were truncated to a maximum of 600 minutes per week (an adaptation of guidelines regarding maximum reports of daily activities to those recommended for the International Physical Activity Questionnaire;[22] a total of 38 responses were truncated). A continuous score was calculated from all items by combining minutes per week spent exercising in each activity. One outlier with 5160 exercise minutes/week was removed. The continuous exercise variable (i.e., total exercise minutes/week) was used for all analyses with baseline exercise. To create a categorical exercise change variable (i.e., change over time), a binary variable was created with a cut-off of ≥ 365 minutes/week, derived from a two-component mixture distribution analysis.[23] This methodology was selected because of a bimodal distribution in the physical activity data (Figure S1 in supporting information). Participants with ≥ 2 study visits were then classified into one of four categories, based on their activity levels at first and last follow-up visits: "decreasers" (moved from ≥ 365 minutes/week to < 365 minutes/week from first to last visit); "stable low" (remained < 365 minutes/week at first and last visits); "stable high" (remained ≥ 365 minutes/week at first and last visits); or "increasers" (moved from < 365 minutes/week to ≥ 365 minutes/week from first to last visit). Quality control was run on these data to ensure participants did not show negligible exercise change (i.e., < 10 minutes/week) that resulted in a category change. Thus, all participants who changed categories did so with an exercise increase or decrease of at least 10 minutes/week. A limitation of this approach is that individuals have varying follow-up lengths, thus one exercise change score may be calculated over 2 years, and one may be over 6 years, depending on how long participants remained in the study. This is a general limitation of dropouts in longitudinal research, and the mean length of follow-up in the current sample was 1.9 ± 2 years.

2.4 | Genotyping, CSF collection, and neuroimaging

Genotyping was performed on DNA extracted from blood samples to identify ADAD genetic mutations on the *APP*, *PSEN1*, or *PSEN2* genes (see Supplementary Methods in supporting information).

Fasting CSF was collected in the morning via lumbar puncture, using previously described methods (Supplementary Methods).[24] Concentrations of CSF Aβ40, Aβ42, total tau (t-tau), and total phosphorylated tau (p-tau181) were measured by chemiluminescent enzyme immunoassay using an automated platform (LUMIPULSE G1200, Fujirebio) according to the manufacturer's specifications.

Brain volume measures were derived from T1-weighted images using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence on a 3T scanner[25] and were matched to the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol.[25] Images were processed using FreeSurfer (Supplementary Methods). A standardized uptake value ratio (SUVR) was calculated for brain Aβ measured using Pittsburgh compound B positron emission tomography (PiB PET) with regional spread function partial volume correction (Supplementary Methods).[26]

2.5 | Statistical analyses

Analyses were conducted using R statistical computing packages version 4.3.1 (R Core Team, 2021). To examine associations between

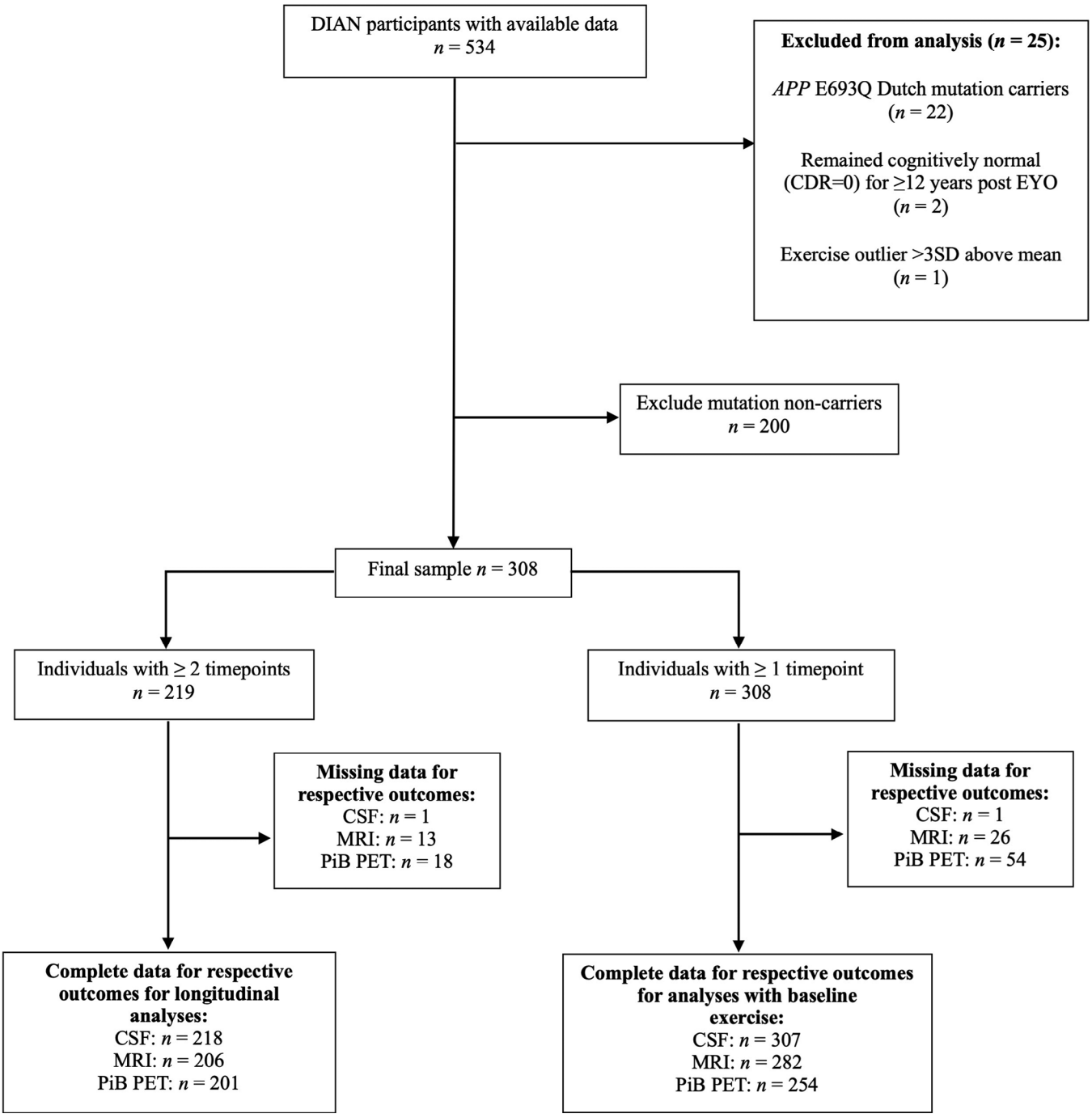

FIGURE 1 Flow diagram indicating number of participants with data available for inclusion for each analysis. Timepoints refer to number of visits at which both exercise and biomarker data were collected. *APP*, amyloid precursor protein; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; DIAN, Dominantly Inherited Alzheimer Network; EYO, estimated years from expected symptom onset; MRI, magnetic resonance imaging; PiB PET, Pittsburgh compound B positron emission tomography; SD, standard deviation

exercise and AD-related biomarkers, a series of linear mixed-effects models (LMMs) were conducted (Supplementary Methods). We examined the interaction between exercise measured at baseline and time (in years) on the dependent variables of CSF Aβ42, CSF Aβ42/Aβ40, CSF p-tau/Aβ42, CSF p-tau181, and CSF t-tau; hippocampal volume, total cortical volume, total gray matter volume, subcortical gray matter volume, and white matter hyperintensities; and PiB PET SUVR measured across multiple follow-up visits. To examine longitudinal change in exercise and AD markers, these models were re-run using our categorical exercise change variable instead of the baseline exercise variable. We then re-ran all models with an added interaction term for baseline EYO (time x exercise x EYO) to examine whether associations differed based on disease stage. Baseline EYO was treated as a continuous variable in all analyses except in the case of brain Aβ because there

TABLE 1 Descriptive statistics for our subsample of the DIAN cohort, mutation carriers only.

	Subset with ≥ 1 visit ($n = 308$)	Subset with ≥ 2 visits ($n = 219$)	Test statistic
Age, years	39.7 (10.8)	40.0 (10.8)	$t = -0.49$
Sex, % female (n)	56.5 (174)	56.2 (123)	$\chi^2 = 0.00$
APOE ε4 allele carriers, % (n)	30.5 (94)	32.0 (70)	$\chi^2 = 0.04$
MMSE score	26.6 (5.4)	27.0 (4.5)	$t = 1.10$
EYO at baseline, years	−7.0 (11.0)	−6.85 (10.9)	$t = -0.25$
Education, years	14.2 (3.0)	14.2 (2.9)	$t = 0.35$
Family mutation			$\chi^2 = 0.36$
PSEN1, % (n)	77.9 (240)	78.1 (171)	
PSEN2, % (n)	7.1 (22)	5.5 (12)	
APP, % (n)	14.9 (46)	16.4 (36)	
Weekly exercise, min	393.7 (342.9)	393.8 (345.2)	$t = 0.001$
Follow-up, number of visits	2.3 (1.2)	2.8 (1.06)	$t = -5.29$**
CSF Aβ42, pg/mL	610.8 (358.58)	619.6 (380.6)	$t = 0.24$
CSF Aβ42/40	0.07 (0.03)	0.07 (0.03)	$t = 0.13$
CSF p-tau181, pg/mL	76.5 (66.56)	80.3 (68.9)	$t = 0.56$
CSF t-tau, pg/mL	509.2 (350.22)	540.0 (368.9)	$t = 0.86$

Note: If not otherwise described, data are presented as mean (standard deviation). CSF, MMSE, and weekly exercise means are at baseline.
[a]Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; *APP*, amyloid precursor protein; CSF, cerebrospinal fluid; DIAN, Dominantly Inherited Alzheimer's Network; EYO, estimated years from symptom onset; MMSE, Mini-Mental State Examination; *PSEN*, presenilin gene; p-tau, phosphorylated tau; t-tau, total tau.
**$P < 0.001$.

was a non-linear association between EYO and Aβ (Figure S2 in supporting information), thus EYO was separated into categories (≤ −15 EYO; $n = 80$; > −15 EYO to 0; $n = 109$; EYO > 0; $n = 94$, Supplementary Methods). All models included a random intercept for participant ID. A random slope was not estimated because many participants in DIAN have only two time points, meaning a random slope could not be accurately identified. Post hoc investigations for our three-way interaction were conducted by creating 5-year "bins" of the baseline EYO variable (i.e., −15 to −10, −9 to −5 years, etc.) and examining at which point the slope of exercise on the respective AD biomarker first became significant. The aim of this split was to balance adequate sample size within each bin while still improving our understanding of these associations. All analyses, except for post hoc, were corrected for multiple comparisons using the false discovery rate for interaction terms within each biomarker.[27]

Studies using DIAN data often include the gene on which a participants' mutation occurs (i.e., *APP*, *PSEN1*, or *PSEN2*) as a covariate, because although all mutations impact Aβ processing, the biological processes are distinct.[28] Additionally, phenotypic expression of cortical Aβ may be related to the specific location of the affected codon.[28] We aimed to statistically account for these differences by ranking specific mutations (e.g., Glu280Gly, Ala79Val, etc.) based on their average parental age of onset within the sample (regardless of kindred). We assigned each mutation a number, with 1 being assigned to the mutation with the youngest average AAO, and 80 having the oldest average AAO. We subsequently split this variable into quantiles (herein referred to as mutation rank) and tested it for inclusion as a covariate in our analyses.

We considered accounting for the decline in exercise levels across the disease course by controlling for CDR score. However, CDR was excluded as a covariate because it has an underlying association with AD outcome variables; its inclusion would result in incorrect model estimation. We have instead included supplementary analyses with CDR score in place of EYO for outcome variables that showed significant interactions (Supplemental Methods and Table S1 in supporting information).

Covariates differed depending on the outcome variable and were selected to maximize model fit. The following covariates were tested for each dependent variable: revisualized age, sex, apolipoprotein E (*APOE*) ε4 status (coded as carriage of at least one ε4 allele = 1, otherwise = 0), the gene on which the mutation exists (family mutation), and our mutation rank variable. The resultant models included different covariates for each outcome variable, namely: CSF variables included revisualized age, *APOE* ε4 status, mutation rank, and family mutation; magnetic resonance imaging (MRI) included revisualized age, sex, mutation rank, family mutation, and intracranial volume; PiB PET (brain Aβ) included only *APOE* ε4 status.

3 | RESULTS

Descriptive data for participants are presented in Table 1. The sample had a mean age of 39.7 ± 10.8 years, 56.5% were female, had a mean weekly exercise level of 382 ± 330.6 minutes, and had a mean of 2.3 ± 1.2 follow-up visits.

TABLE 2 Partially standardized beta coefficients from linear mixed models examining exercise on Alzheimer's disease-related biomarkers at baseline, over time, and across EYO.

Outcome variable	Baseline exercise Model 1 β (SE)	Baseline exercise x time Model 1 β (SE)	Baseline exercise x time x EYO Model 2 β (SE)	Exercise change category x time Model 3 β (SE)	Exercise change category x time x EYO Model 4 β (SE)
CSF Aβ42	0.08 (0.06)	0.02 (0.02)	0.00 (0.02)	−0.03 (0.02)	0.02 (0.02)
CSF Aβ42/Aβ40	0.05 (0.06)	−0.01 (0.01)	0.01 (0.02)	−0.03 (0.01)	0.02 (0.02)
CSF p-tau/Aβ42	−0.14 (0.06)*	−0.02 (0.01)	−0.01 (0.02)	0.01 (0.01)	−0.02 (0.01)
CSF p-tau	−0.16 (0.06)**	−0.01 (0.01)	−0.01 (0.02)	−0.00 (0.01)	−0.01 (0.02)
CSF t-tau	−0.21 (0.06)***	0.01 (0.02)	−0.00 (0.02)	−0.02 (0.02)	−0.03 (0.02)
Right hippocampal volume	0.12 (0.06)	0.04 (0.01)*	0.06 (0.01)***	0.04 (0.02)*	0.00 (0.01)
Left hippocampal volume	0.14 (0.06)	0.04 (0.02)*	0.06 (0.02)*	0.04 (0.02)	−0.00 (0.02)
Total cortical volume	0.11 (0.04)*	0.01 (0.01)	0.03 (0.01)*	0.01 (0.01)	0.03 (0.01)*
Total subcortical gray matter volume	0.12 (0.05)*	0.01 (0.01)	0.03 (0.01)*	0.01 (0.01)	0.01 (0.01)
Total gray matter volume	0.12 (0.04)*	0.01 (0.01)	0.03 (0.01)*	0.01 (0.01)	0.03 (0.01)*
White matter hyperintensities	−0.10 (0.06)	−0.00 (0.02)	0.01 (0.02)	−0.05 (0.02)	−0.01 (0.02)
Aβ (PiB)	−0.18 (0.06)**	−0.02 (0.01)*	0.04 (0.01)***	−0.00 (0.01)	0.01 (0.01)

Note. All results presented as partially standardized beta coefficient (standard error). Predictor variables are standardized; outcome variables are not. Separate models run for each outcome variable. Significant results reported here have been corrected for multiple comparisons using FDR, applied within each outcome variable (i.e., for CSF 5 outcomes x 4 models = 20 *P* values corrected). FDR correction was applied to the highest order interaction term only (i.e., FDR was not applied to main effects from the same model for Models 1 and 3). Data for the main effect of exercise and exercise x time taken from the same model. All CSF and PiB outcome variables were log transformed. Covariates are as follows CSF: age, *APOE* ε4 status, mutation rank, family mutation; MRI: age, sex, intracranial volume, mutation rank, family mutation; PiB: *APOE* ε4 status; Exercise categories were created based on a 365 minute/week cut-off and classified as 1 = decreased, 2 = remained low, 3 = remained high, 4 = increased, based on follow-up data.
Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; CSF, cerebrospinal fluid; EYO, estimated years from expected symptom onset; FDR, false discovery rate; MRI, magnetic resonance imaging; PiB, Pittsburgh compound B; p-tau, phosphorylated tau; SE, standard error; t-tau, total tau; β, partially standardized beta coefficient.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$ (q values, i.e., FDR corrected, for interaction terms).

3.1 | CSF markers

3.1.1 | Baseline exercise and CSF biomarkers across time and EYO

Higher self-reported exercise was associated with lower p-tau/Aβ42, p-tau, and t-tau cross-sectionally; however, these associations did not persist over time (Table 2; Model 1). There were no interactions between baseline exercise, time, and EYO on any CSF marker (Table 2; Model 2).

3.1.2 | Change in exercise and CSF biomarkers across time and EYO

Exercise change category was not associated with CSF Aβ42, Aβ42/40, p-tau/Aβ42, p-tau, and t-tau rates of change (Table 2; Model 3). There was no significant interaction for change in exercise, time, and EYO on any CSF marker (Table 2; Model 4).

3.2 | MRI

3.2.1 | Baseline exercise and MRI variables across time and EYO

Greater baseline exercise was associated with greater total brain volume, subcortical volume, and total gray matter volume cross-sectionally, but the slopes of brain volume change over time were not associated with baseline exercise (Table 2; Model 1). For hippocampal volume, there was no cross-sectional association with exercise; however, greater baseline exercise was associated with a slower decline in right and left hippocampal volume over time (not considering EYO; Table 2; Model 1).

There were significant interactions between baseline exercise, time, and EYO for every MRI outcome except white matter hyperintensities (Table 2; Model 2). These associations show that higher baseline exercise relates to slower decline in brain volume and that this becomes increasingly more pronounced as individuals move closer to, and beyond, their predicted EYO (Figure 2; only right hippocampal

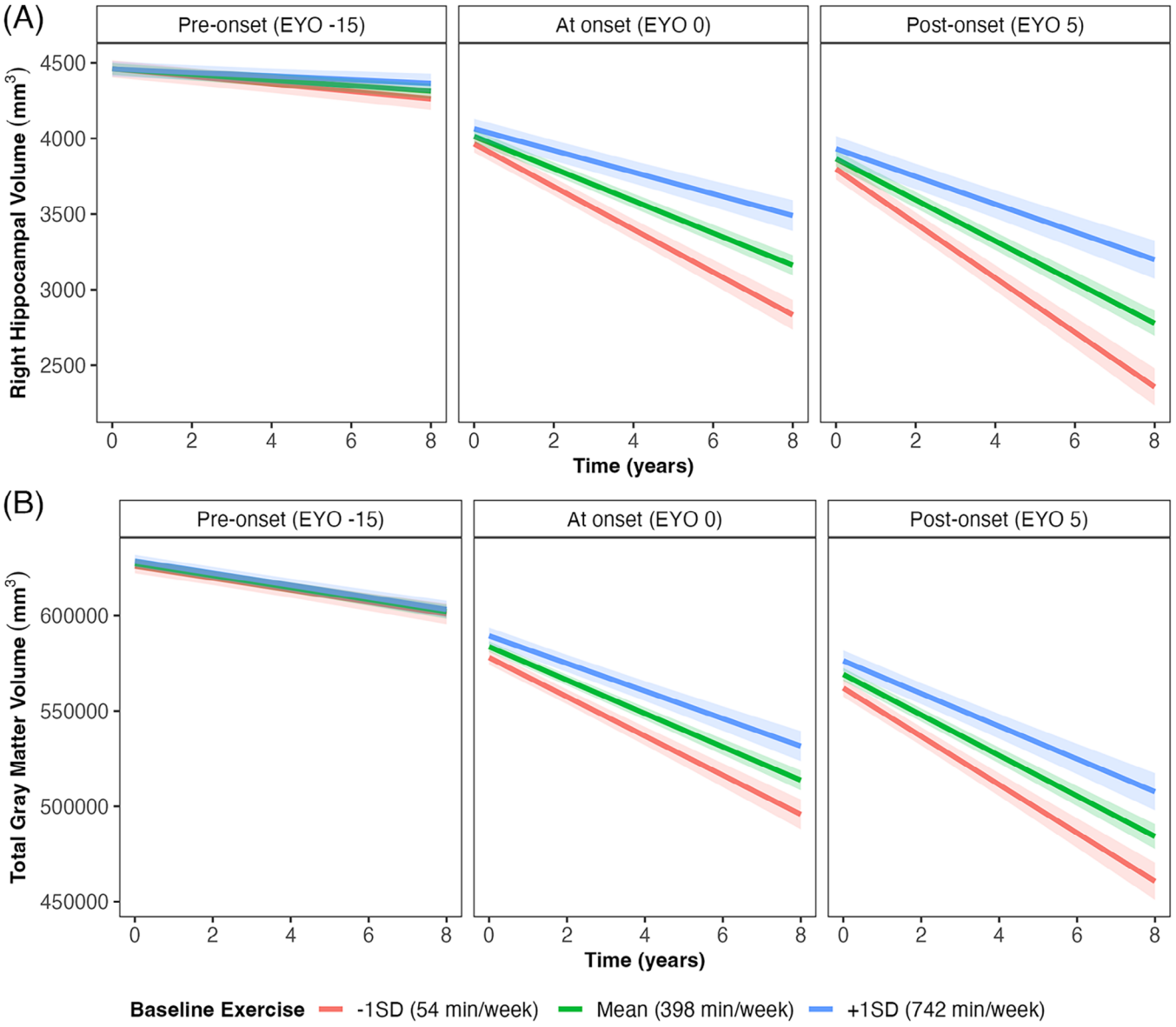

FIGURE 2 Baseline exercise x time interaction on structural brain outcomes at baseline EYO. Baseline EYO was treated as a continuous variable in all models and is only separated here for visual aid (i.e., EYO groups were not created); a negative EYO represents years before estimated symptom onset, positive EYO represents years post estimated symptom onset. The data presented here are fitted values from analyses modeling associations between exercise and brain outcomes given a particular EYO. Scatterplots of raw data are presented in Figure S4 in supporting information. The left-hand panel shows the fitted values for change in brain volume over time if EYO is −15, the middle demonstrates the association if EYO is 0, and the right shows this association if EYO is 5. Gray bands show 95% confidence intervals. A, Right hippocampal volume. B, Total gray matter volume. EYO, estimated years from expected symptom onset; SD, standard deviation

volume and total gray matter volume included here, other outcomes demonstrate a similar pattern and are included in Figure S3 in supporting information). Additional analyses indicated that the associations between exercise and structural brain outcomes were first observed at −5 EYO (i.e., 5 years before predicted onset), and were maintained up to 15 years post estimated symptom onset (*P* value range from < 0.001 – 0.023). Figure S4 in supporting information shows scatterplots for the raw uncorrected values by exercise group across EYO. There were no significant interactions between baseline exercise x time for any volumetric outcome within CDR groups when replacing EYO with CDR (Table S1).

3.2.2 | Change in exercise and MRI variables across time and EYO

Those who maintained high exercise retained greater hippocampal volume over time compared to those who decreased their exercise

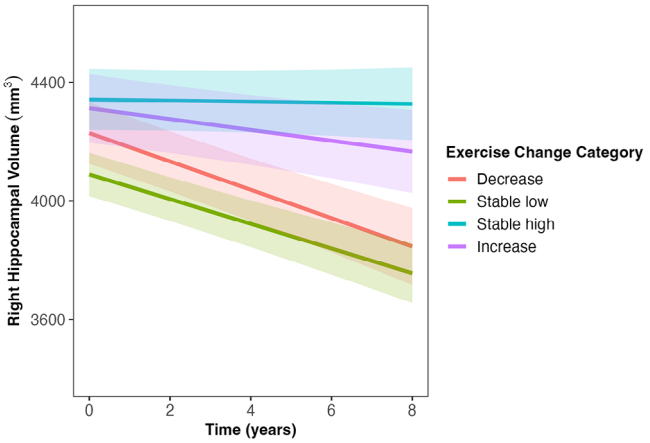

FIGURE 3 Association between change in exercise and change in right hippocampal volume over time. Exercise categories were created based on a 365 minutes/week cut off and classified as: 1 = "decreasers," 2 = "stable low," 3 = "stable high," 4 = "increasers," based on follow-up data. Differences exist between "decreasers" versus "stable high category," $\beta = 0.13$, SE = 0.05, $P = .006$ and "stable low"' versus "stable high" category, $\beta = 0.11$, SE = 0.04, $P = = 0.006$. Gray bands represent 95% confidence intervals. EYO, estimated years from expected symptom onset; SE, standard error

(Table 2, Figure 3; decreases as a reference, $\beta = 0.13$, standard error [SE] = 0.05, $P = 0.006$). There were significant interactions between changes in exercise, time, and EYO for total cortical volume and total gray matter volume (Table 2; Model 4; Figure 4). Those who maintained stable high exercise or increased exercise had slower decline in total cortical volume compared to those who decreased their exercise level ("stable high": $\beta = 0.08$, SE = 0.04, $P = 0.028$; "increasers": $\beta = 0.08$, SE = 0.04, $P = 0.041$), an effect that became more pronounced across EYO (Figure 4). A similar pattern was shown for total gray matter volume; however, individual comparisons between exercise categories were only trending toward significance ("decreasers" vs. "stable high": $\beta = 0.06$, SE = 0.03, $P = 0.065$; "decreasers" vs. "increasers": $\beta = 0.07$, SE = 0.04, $P = 0.060$; Figure 4).

3.3 | Brain Aβ

3.3.1 | Baseline exercise and brain Aβ across time and EYO

Higher self-reported baseline exercise was associated with lower brain Aβ as measured by PiB PET, both cross-sectionally and over time (Table 2; Model 1). There was an interaction between baseline exercise, time, and EYO (Table 2; Model 2). Results showed that in the pre-onset group (see Statistical Methods), greater exercise was associated with slower accumulation of Aβ ($\beta = -0.16$, SE = 0.04, $P < 0.001$; Figure 5). However, there was a trend for the opposite pattern in those nearing predicted onset, that is, those with high baseline exercise showed greater Aβ accumulation ($\beta = 0.06$, SE = 0.03, $P = 0.067$; Figure 5). In those past their predicted onset (i.e., EYO > 0), there was no interaction between exercise and time on brain Aβ ($\beta = -0.01$, SE = 0.02, $P = 0.582$; Figure 5). We examined demographic differences between our EYO groups to further understand these findings (Table S2 in supporting information). There were differences between EYO groups only for age and family mutation (Table S2); however, when adding these variables to the baseline exercise x time on PiB model for our nearing predicted onset group, results remained similar ($\beta = 0.06$, SE = 0.03, P$p = 0.070$). Figure S4 (panel f) shows scatterplots for the raw uncorrected and untransformed brain Aβ values by exercise group across EYO; Table S1 shows these analyses separated by CDR score instead of EYO (i.e., baseline exercise x time within CDR groups), none of which were significant.

3.3.2 | Change in exercise and brain Aβ across time and EYO

Change in exercise was not associated with brain Aβ over time, and there was no interaction with EYO (Table 2; Models 3 and 4).

4 | DISCUSSION

The primary aim of the current study was to examine associations between exercise levels and AD-related biomarkers in ADAD mutation carriers. We report cross-sectional associations between greater exercise participation and lower CSF measures of p-tau, t-tau, p-tau/Aβ42, greater brain volume, and lower brain Aβ burden; and longitudinal associations between greater exercise and slower brain atrophy and Aβ accumulation, which varied dependent upon disease stage. These results illustrate consistent associations between exercise and AD-related biomarkers, and although a causal relationship cannot be determined, they support the notion of additional randomized controlled trials investigating the therapeutic potential for exercise to delay the onset of AD.

Cross-sectional analyses revealed associations between exercise and CSF markers, brain volume, and brain Aβ, all in the expected directions. These results are consistent with previous cross-sectional research in the DIAN cohort, which showed associations between greater exercise and lower brain Aβ,[17], less AD-like CSF pathology, and better cognitive function.[18] In the current study, CSF markers were the only outcome that did not demonstrate longitudinal associations with exercise levels. Previous research within the DIAN cohort showed the greatest change in CSF markers > 5 to 10 years before EYO, and a slowing of these changes (or reversal in the case of p-tau, which shows a significant decline) as individuals moved toward EYO.[24,29] This pattern was not observed in prior DIAN studies for other biomarkers such as brain Aβ and hippocampal volume, which steadily increased or decreased (respectively) over the disease course.[26] In the current study, the average EYO at baseline was 7.0 years before symptom onset, which is just before changes in CSF markers may begin to

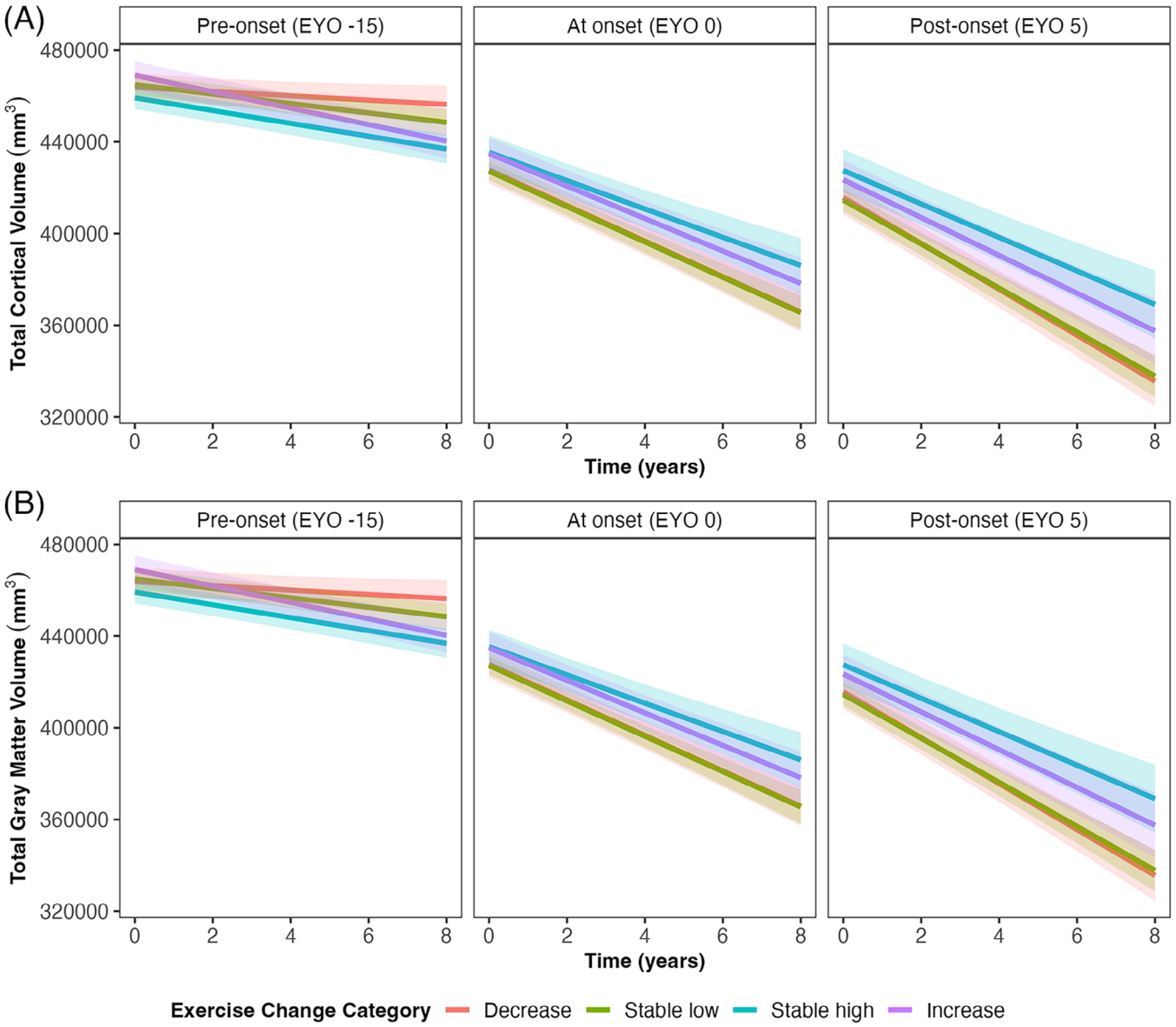

FIGURE 4 Change in exercise on structural brain outcomes over time and across EYO. Exercise categories were created based on a 365 minute/week cut off and classified as: 1 = "decreasers," 2 = "stable low," 3 = "stable high," 4 = "increasers," based on follow-up data. EYO was treated as a continuous variable in all models and is only separated here for visual aid. Gray bands represent 95% confidence intervals. Total cortical volume, differences exist between decreasers versus stable high category, $\beta = 0.08$, SE = 0.04, $P = .028$; and decreasers versus increasers, $\beta = 0.08$, SE = 0.04, $P = .041$. Total gray matter volume, a trend exists for differences between decreasers versus stable high: $\beta = 0.06$, SE = 0.03, $P = .065$, and decreasers versus increasers: $\beta = 0.07$, SE = 0.04, $P = .060$. EYO, estimated years to symptom onset; SE, standard error

plateau.[30] Thus, exercise may have a greater influence on CSF markers earlier in the disease stage when they are more variable and sensitive to change.

Greater exercise was associated with a slower decline in brain volume over time; this association was evident as individuals moved toward, and beyond, their EYO; however, the effect size was relatively small. Associations between higher exercise and greater brain volume were first observed 5 years before EYO and were maintained up to 15 years post symptom onset. This is consistent with previous research in the DIAN cohort showing hippocampal atrophy begins ≈ 5 years before diagnosis.[29] Similarly, previous research in older adults at risk for late-onset AD (LOAD; which may be comparable to ADAD because of similarities in pathophysiology[31–33]) has demonstrated beneficial effects of exercise on the hippocampus,[8,34] although recent meta-analyses have reported inconsistent findings for this association.[11,35] One reason for this inconsistency may be, as demonstrated in the current results, that exercise is only associated with AD biomarkers during times of greatest pathology-related change (i.e., ≤ 5 years before symptom onset for MRI outcomes, and > 5 years before symptom onset for CSF), and pathological change, or lack thereof, is often difficult to

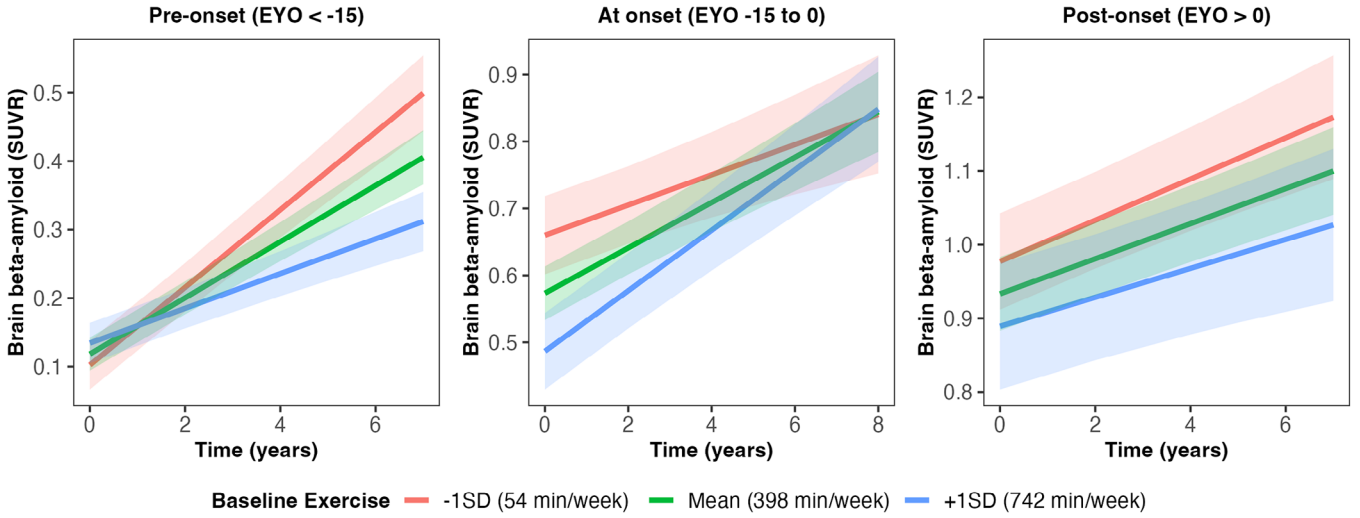

FIGURE 5 Baseline exercise x time on brain Aβ (log) in subsets of EYO stages (i.e., EYO groups were created). Data were subset based on EYO because of a non-linear association between EYO and brain Aβ (Figure S2 in supporting information). The left panel demonstrates the change in Aβ over time separated by exercise level within the pre-onset group ($n = 80$), the middle panel demonstrates change over time in those nearing EYO ($n = 109$), the right panel demonstrates those post EYO ($n = 94$). Gray bands represent 95% confidence intervals. Aβ, amyloid beta; EYO, estimated years from expected symptom onset; SD, standard deviation

determine in individuals at risk for LOAD. Thus, to better understand the utility of exercise as a therapeutic strategy, future studies in LOAD should consider enriching for individuals likely on the AD trajectory (e.g., those accumulating brain Aβ), identified using proxy measures such as CSF or plasma markers.[36] Such studies will improve our understanding of the efficacy of exercise in influencing biomarker changes in preclinical AD.

Baseline exercise was associated with slower brain Aβ accumulation ≥ 15 years before estimated symptom onset; however, there was no association between exercise and brain Aβ nearing, and post-, estimated symptom onset. This is consistent with previous research from both LOAD and ADAD studies indicating that brain Aβ begins to accumulate up to 20 years before dementia diagnosis[29,37] and the notion that lifestyle interventions should be implemented at early disease stages, before Aβ-associated inflammation and neuronal damage become irreversible.[38] It is noteworthy, however, that Aβ accumulation in ADAD individuals likely cannot be prevented due to mutations with near 100% penetrance, but may be delayed via exercise. Although the current results are derived from younger individuals with ADAD mutations, they may be generalizable to individuals with LOAD due to strong pathological similarities.[33] The current study supports the notion that lifestyle interventions to delay the onset of LOAD may be best implemented in midlife and early aging (i.e., in the sixth decade of life).

The current study used a self-report measure of exercise. Although this measure has been previously validated,[17] it may be subject to bias and fallible memory. The American Heart Association recommends 150 minutes of moderate-intensity exercise per week; the thresholds in the current study were high compared to those recommendations. This is likely attributed to either an overreporting of actual physical activity levels (on average 44% in other populations)[39] or increased activity levels because those in the DIAN cohort may be acutely aware of AD risk factors and attempt to mitigate them. The current study did, however, use high-quality measures of brain structure, function, and underlying pathology, and used a comprehensive approach to statistical analyses. Due to the observational design, we are not able to determine causality from our results, and indeed, declines in functioning or increases in pathology may contribute to decreased exercise levels. We attempted to better understand these associations by examining exercise and AD biomarkers at different CDR levels (Table S1); however, this analysis is limited by group sample sizes and restricted granularity because the CDR has a limited range (five possible scores). Finally, the effect sizes (standardized betas) of our results are relatively small, and lifetime exercise habits which we were not able to account for may have influenced current findings. Thus, randomized controlled trials are required to confirm our results and determine the magnitude of potential clinical benefit.

Here, we demonstrate that greater exercise is associated with benefits for multiple AD-related outcomes including CSF biomarkers, brain structure, and brain Aβ (only at preclinical stages) in those who carry ADAD mutations. Exercise is worthy of further investigation (using randomized controlled trials) as a potential strategy to alter AD trajectory, whether it be ADAD or sporadic AD, and preserve brain structure and function after AD onset.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

All participants and collateral sources provided written informed consent prior to any study-related procedures.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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