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Featured Article

Habitual exercise levels are associated with cerebral amyloid load in presymptomatic autosomal dominant Alzheimer's disease

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[1] http://www.dian-info.org/personnel.htm.

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Abstract

Introduction: The objective of this study was to evaluate the relationship between self-reported exercise levels and Alzheimer's disease (AD) biomarkers, in a cohort of autosomal dominant AD mutation carriers.

Methods: In 139 presymptomatic mutation carriers from the Dominantly Inherited Alzheimer Network, the relationship between self-reported exercise levels and brain amyloid load, cerebrospinal fluid (CSF) $A\beta_{42,}$ and CSF tau levels was evaluated using linear regression.

Results: No differences in brain amyloid load, CSF $A\beta_{42}$, or CSF tau were observed between low and high exercise groups. Nevertheless, when examining only those already accumulating AD pathology (i.e., amyloid positive), low exercisers had higher mean levels of brain amyloid than high exercisers. Furthermore, the interaction between exercise and estimated years from expected symptom onset was a significant predictor of brain amyloid levels.

Discussion: Our findings indicate a relationship exists between self-reported exercise levels and brain amyloid in autosomal dominant AD mutation carriers.

Keywords: Physical activity; Amyloid β; Genetics; Tau; Alzheimer's disease; Dementia

1. Introduction

Deposition of amyloid plaque within the brain contributes to the neuronal and synaptic loss consistent with Alzheimer's disease (AD), whereas hyperphosphorylation of tau, believed to occur downstream of amyloid plaque formation, is associated with AD symptom severity [1]. Autosomal dominant AD (ADAD) caused by a mutation in one of three genes, amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*), is a rare form of AD resulting in the alteration of amyloid β (Aβ) processing, leading to AD with full penetrance and at an early age (typically <50 years). In both sporadic late-onset AD (LOAD) and ADAD, accumulation of amyloid manifests up to two decades before the presentation of clinical symptoms [2,3], thus, providing a window of opportunity for intervention. However, in both LOAD and ADAD, there are currently no available pharmaceutical treatments known to alter the trajectory of brain amyloid accumulation, nor significantly alter the course of cognitive decline.

Numerous observational studies indicate that high levels of physical activity are associated with reduced risk of clinical LOAD [4–7], as well as risk of LOAD mortality [8]. It is likely that this association is governed by underlying mechanisms, including an effect of physical activity on Aβ and/or tau. Indeed, animal studies have demonstrated that both soluble and insoluble Aβ levels are lowered by exercise in AD transgenic mice [9–15]. Within the small number of human studies, greater levels of self-reported physical activity have been associated with lower levels of brain amyloid, as measured through amyloid-binding tracers coupled with positron emission tomography (PET) [16–18]. Furthermore, Liang et al. [16] reported that higher physical activity levels in older adults were associated with greater levels of cerebrospinal fluid (CSF) $A\beta_{42}$ (an indicator of lower brain amyloid) and lower levels of CSF tau (a marker of neuronal injury). The evidence that exercise is associated with lower brain amyloid levels and less neuropathology reflected by CSF Aβ and tau measurements provides important insight into the possible use of exercise as a therapeutic modality in AD. These associations, however, are yet to be examined in individuals with mutations causing ADAD, a gap in knowledge that the present study seeks to address.

The ADAD mutation carriers in the Dominantly Inherited Alzheimer Network (DIAN) study [2] provide an excellent model to determine whether exercise is associated with amyloid load, as these mutation carriers are destined to accumulate cerebral amyloid at an early age. In the present study, we explored relationships between self-reported exercise habits, AD mutation carrier status, and AD biomarkers, hypothesizing the following among presymptomatic ADAD mutation carriers: (1) exercise habits are associated with biomarker evidence of Aβ and tau (as measured by brain amyloid, CSF $A\beta_{42}$, and CSF tau), (2) among individuals with evidence of brain amyloid, those with higher amounts of exercise would demonstrate less evidence of AD biomarkers, and (3) exercise level modifies the relationship between expected age of AD symptom onset and AD biomarkers. We also investigated the association between exercise and AD neuroimaging and CSF biomarkers, as described previously, in mutation noncarriers included in the DIAN observational study, to evaluate this relationship in those with similar demographic characteristics but without a dominant gene mutation.

2. Methods

2.1. Participants

Participants at risk for carrying an ADAD mutation were enrolled in the DIAN study. To be eligible for the DIAN study, participants were recruited only if they were members of a family pedigree with known ADAD mutations, with 197 families (from USA, UK, Australia, Japan, Germany, and Argentina) comprising the DIAN

cohort. Information regarding participant enrollment and procedures has previously been described in detail [2]. In the current cross-sectional analysis, we used baseline data from mutation noncarriers and mutation carriers with no cognitive impairment. From DIAN data freeze-10, a total of 435 (mutation noncarriers = 172, mutation carriers = 263) participants had baseline data. Individuals with missing exercise and PET data, and/or a Clinical Dementia Rating Global score of greater than 0 were excluded from the analysis (see Fig. 1 for full description of participant numbers). Participants without available CSF data, but with available PET data, were included in the brain amyloid analyses only. All participants underwent a comprehensive clinical assessment regarding self and family medical history, medication use, and a physical/medical examination.

2.2. Neuroimaging

Images obtained through PET with the use of Pittsburgh compound B (PiB; an Aβ-binding ligand) were coregistered with individual magnetic resonance images for the identification of regions of interest. All studies were collected contemporaneously to baseline determination of self-reported exercise. For each region of interest (FreeSurfer defined, MA, USA), a standardized uptake value ratio (SUVR) was calculated with the cerebellar cortex used as the reference region [19]. The SUVRs of the prefrontal cortex, temporal lobe, gyrus rectus, and precuneus were averaged to calculate a total cortex SUVR. An SUVR of 1.3 was used to stratify the cohort based on amyloid positivity (PiB− $<$ 1.3, PiB+ $\geq$ 1.3) [20].

2.3. CSF collection and biochemical analyses

Fasting CSF was collected in the morning via lumbar puncture. Samples were snap frozen and shipped on dry ice to the DIAN Biomarker Core Laboratory. Levels of $A\beta_{42}$ and total tau were measured by immunoassay (INNO-BIA AlzBio3, Innogenetics, Ghent, Belgium). All values included in the analysis met quality control standards, which included a coefficient of variation of 25% or less (typical % coefficients of variation were $<$10%), kit "controls" within the expected range, and measurement consistency between plates of a common sample included in each run.

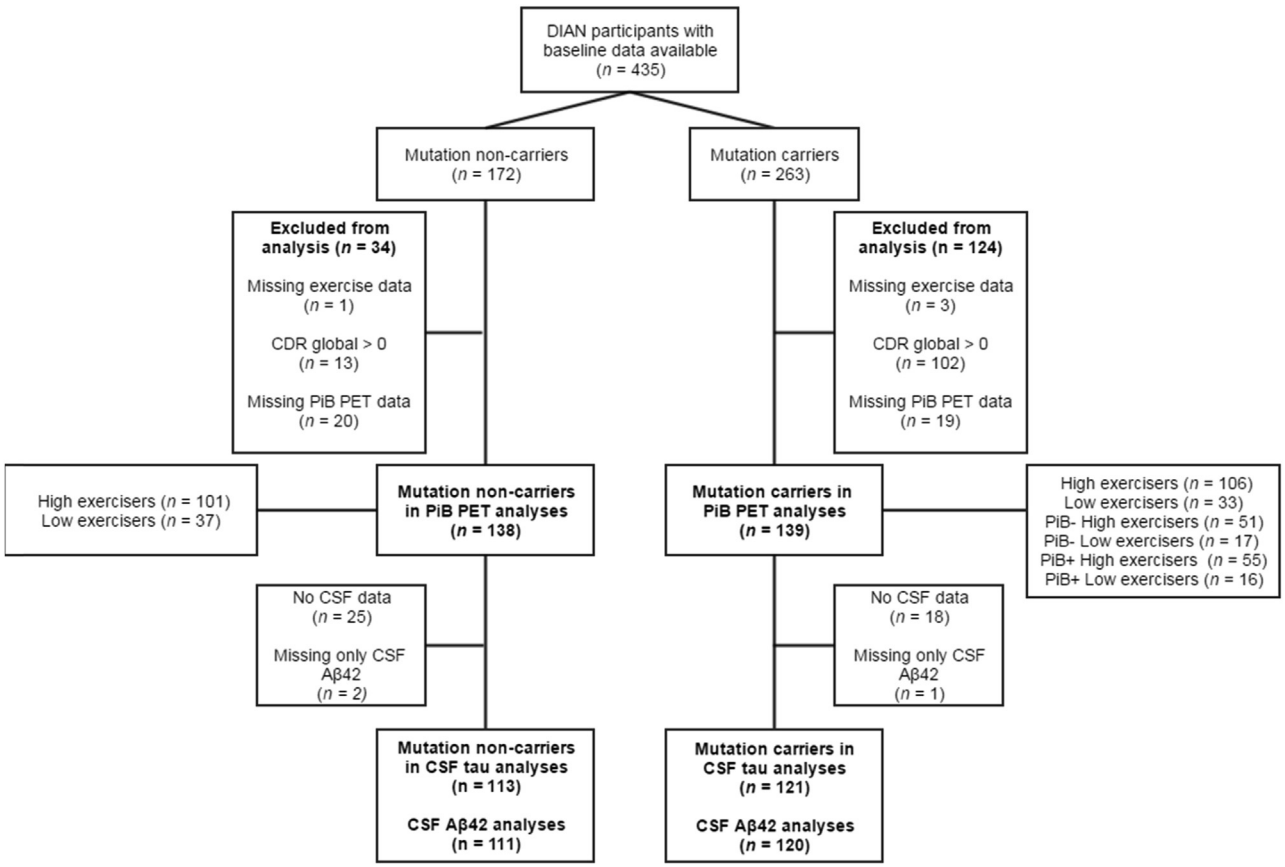

Fig. 1. Flow diagram indicating number of participants with data available for inclusion in this study. Low exercisers reported less than 150 minutes per week of exercise, whereas high exercisers reported 150 or more minutes of exercise per week. Abbreviations: Aβ, amyloid β; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; DIAN, Dominantly Inherited Alzheimer Network; PiB−, PiB negative with an SUVR $<$1.3; PiB+, PiB positive with an SUVR $\geq$1.3; PiB PET, Pittsburgh compound B positron emission tomography.

2.4. Genotyping

For the identification of ADAD genetic mutations in the *APP*, *PSEN1*, or *PSEN2* genes, genotyping was performed on extracted DNA from blood samples. Genotyping was performed at the Genome Technology Access Centre at Washington University using the Infinium HumanExomeCore V1.0 Beadchip (Illumina, Inc, USA). Genotype data were cleaned by applying a minimum call rate for single-nucleotide polymorphisms and individuals, set at 98%.

2.5. Exercise level evaluation

Participants reported, via questionnaire, their average time spent partaking in 10 various leisure-time exercise activities over the past 12 months in a measurement of "minutes per week." This exercise questionnaire has not been previously validated; thus, using data available from DIAN participants reporting exercise at baseline and at a 1-year follow-up ($n = 107$), we assessed the consistency of exercise reports in this cohort and reported a significant correlation with a moderate effect size ($r = 0.53$, $P < .0001$). Participation in activities such as walking, running, cycling, swimming, tennis, aerobics, and weight training was recorded. In the questionnaire instructions, participants were encouraged to have their responses corroborated by their collateral source (e.g., family member or friend). Outliers were minimized by truncation of individual item responses to a maximum of 600 minutes per week (an adaptation of similar guidelines regarding maximum reports of daily activities to those recommended for the International Physical Activity Questionnaire [21]); this truncation did not alter categorization into the exercise groups (described subsequently). A continuous score was calculated from all items by the addition of minutes per week spent exercising in each activity. This continuous score was stratified based on current recommendations from the World Health Organization and the American College of Sports Medicine of a minimum of 150 minutes per week of exercise [22,23]. Individuals reporting less than 150 minutes of exercise per week were categorized into a "low exercise" group (mutation noncarriers, $n = 37$; mutation carriers, $n = 33$), and those participating in more than or equal to 150 minutes of activity per week were categorized into a "high exercise" group (mutation noncarriers, $n = 101$; mutation carriers, $n = 106$).

2.6. Statistical analysis

Estimates years from expected symptom onset (EYO) was calculated using previously published mutation data, if available; if data for a specific mutation were not available, then the parental age of symptom onset was used. The specified age of symptom onset from previously published data (or if unavailable, parental age of onset) was taken from the participant's age at the time of assessment to calculate EYO (e.g., a participant aged 30 years at assessment, minus previously published age of symptom onset, 37 years: EYO = −7, i.e., 7 years to expected symptom onset). Because of the high collinearity between EYO and age ($r = 0.79$, $P < .0001$), the age variable was residualized from EYO for use as a covariate in the linear models. Descriptive data were calculated in the form of mean (standard deviation) and percentage (n) for important clinical and demographic data. Independent sample t tests were used to evaluate differences in continuous variables, and chi-square tests were used to calculate differences in categorical variables, between the low and high exercise groups for both mutation noncarriers and mutation carriers.

Following the stratification of the study cohort into mutation noncarriers and mutation carriers, a series of linear models was used to examine differences in brain amyloid burden and CSF biomarker levels between the low and high exercise groups. These analyses were conducted in the mutation noncarriers to examine whether associations observed in the mutation carriers were unique to this genetic status or common to all individuals of a similar age group regardless of genetic status. Brain amyloid burden, CSF Aβ, and CSF tau were entered individually as dependent variables, with exercise group entered as a dichotomous-independent variable. Furthermore, age (residualized from EYO), family mutation (i.e., *APP*, *PSEN1*, or *PSEN2*), and EYO were entered as covariates in all models, with the inclusion of an exercise group*EYO interaction. The mutation carrier group was further stratified into those who were PiB− versus those who were PiB+, and the models were rerun. The number of participants in each group and stratified groupings is described in detail in Fig. 1.

All statistical analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, version 22.0; IBM Corp, Armonk, NY, USA). A P value of .05 or smaller determined a significant result. False discovery rate (FDR; R environment, version 3.3.2) was used for group corrections for multiple comparisons [24]. Data were visually inspected for outliers and all data points were within 3.29 standard deviation of the mean, a cutoff described by Tabachnick and Fidell [25]. Values for individual participants are not displayed on graphs (i.e., as a scatterplot) to protect the confidentiality of the mutation status of participants (e.g., based on EYO alone, a participant could potentially deduce their mutation status).

3. Results

3.1. Descriptive statistics

Descriptive statistics related to demographics and relevant medical history are detailed in Table 1. No differences were observed between the low and high exercise groups within the mutation noncarriers. The mutation carrier low exercise group (38.6 ± 7.9 years) was significantly older than the mutation carrier high exercise group

Table 1
Demographic and clinical cohort characteristics stratified by noncarriers and carriers of autosomal dominant Alzheimer's disease mutations, split by exercise level

Variable	NC low exercise (n = 37)	NC high exercise (n = 101)	NC low exercise versus NC high exercise* P value	MC low exercise (n = 33)	MC high exercise (n = 106)	MC low exercise versus MC high exercise* P value
Age, years	39.2 ± 11.6	39.0 ± 11.3	.94	38.6 ± 7.9	33.7 ± 9.3	.008
EYO	N/A	N/A	N/A	−10.2 ± 9.4	−13.6 ± 9.2	.07
Years of education	15.0 ± 3.2	14.9 ± 2.5	.89	14.9 ± 2.8	14.7 ± 2.8	.66
Gender, female % (n)	65 (24)	56 (57)	.37	64 (21)	56 (59)	.42
APOE ε4 allele carriers, % (n)	21.6 (8)	30.7 (31)	.29	36.4 (12)	25.7 (27)	.24
PiB SUVR	1.03 ± 0.08	1.05 ± 0.07	.21	1.77 ± 1.03	1.59 ± 0.64	.23
PiB+[†],% (n)	0 (0)	0 (0)	N/A	49 (16)	52 (55)	.73
GDS	1.4 ± 1.7	1.3 ± 1.6	.66	2.2 ± 2.2	1.4 ± 1.8	.04
BMI, kg/m^2	29.3 ± 8.7	29.4 ± 9.8	.96	29.8 ± 9.6	27.2 ± 6.2	.07
High cholesterol, % (n)	11 (4)	17 (17)	.54	21 (7)	12 (13)	.24
Hypertension, % (n)	13 (5)	18 (18)	.82	12 (4)	5 (5)	.13
Exercise duration/week, minutes	68 ± 43	427 ± 218	<.001	64 ± 51	522 ± 343	<.001
Mutation carriers, *APP*/*PSEN1*/*PSEN2* (n)	N/A	N/A	N/A	17/7/9	85/9/12	

Abbreviations: APOE, apolipoprotein E; APP, amyloid precursor protein; BMI, body mass index; EYO, estimated years from expected symptom onset; GDS, Geriatric Depression Scale; MC, mutation carriers; NC, mutation noncarriers; PiB SUVR, Pittsburgh compound B standardized uptake value ratio; PSEN1, presenilin 1; PSEN2, presenilin 2.

NOTE. Unless otherwise described, data are presented as the mean ± standard deviation of the mean.

*From independent samples t test for continuous variables and chi-square test for categorical variables.

[†]Those with PiB SUVR 1.3 and greater were categorized as PiB positive (PiB+).

(33.7 ± 9.3 years; t = 2.68, P = .008). Depressive symptoms (as measured by the Geriatric Depression Scale [GDS]) were significantly higher among the mutation carrier low exercise group (2.2 points ± 2.2 points) compared with the mutation carrier high exercise group (1.4 points ± 1.8 points; t = 2.04, P = .04). To evaluate the effect of depressive symptoms on the relationship between exercise and AD neuroimaging and CSF biomarkers, GDS was entered as a covariate into the models reported in Tables 2-4; however, the inclusion of GDS did not alter the findings (data not reported), and thus this variable was not included in the final analysis.

3.2. The impact of exercise on Aβ and tau

Within the mutation noncarriers (Table 2), no differences in PiB SUVR (F = 0.33, P = .60), CSF Aβ_{42} (F = 1.48, P = .23), and CSF tau (F = 2.26, P = .14) were evident between the low and high exercise groups. On examination of all mutation carriers (Table 3), there were also no differences in PiB SUVR (F = 2.68, P = .10), CSF Aβ_{42} (F = 0.01, P = .95), and CSF tau levels (F = 0.25, P = .62) between the low and high exercise groups. To examine only those individuals in whom significant brain amyloid load was already present, we stratified the mutation carriers based on PiB positivity (cut-off = 1.3) and reran the linear models. In the PiB+ group, lower brain amyloid burden was observed in the mutation carrier high exercisers (SUVR = 2.16 ± 0.15) compared with the mutation carrier low exercisers (SUVR = 2.36 ± 0.19; F = 8.20, P = .006, FDR-adjusted P = .018).

Previous studies have reported an effect of the *APOE* ε4 allele on the relationship between exercise and brain amyloid in LOAD; thus, we reran the linear models including

Table 2
Mutation noncarriers: results from linear models, examining the differences in Pittsburgh compound B positron emission tomography–measured brain amyloid burden and CSF biomarkers between the low and high exercise groups (models also included family mutation, EYO, age, and an EYO*exercise interaction)

	Exercise*					Family mutation[†]			EYO[†]			Age[‡]			EYO*exercise		
	Low exercise	High exercise															
Dependent variable	Mean (SE)[§]	Mean (SE)[§]	F	P	η_p^2	F	P	η_p^2	F	P	η_p^2	F	P	η_p^2	F	P	η_p^2
PiB SUVR (n = 138)	1.03 (0.01)	1.04 (0.01)	0.33	.60	0.003	1.53	.22	0.023	2.64	.11	0.020	1.71	.19	0.013	0.43	.51	0.003
CSF Aβ_{42} (ng/L) (n = 111)	387.2 (29.1)	439.6 (18.0)	1.48	.23	0.014	1.13	.33	0.021	0.65	.42	0.006	2.74	.10	0.026	0.01	.97	0.001
CSF tau (ng/L) (n = 113)	53.0 (4.8)	60.4 (3.0)	2.26	.14	0.021	1.40	.25	0.026	2.78	.10	0.026	0.04	.84	0.001	0.64	.43	0.006

Abbreviations: CSF, cerebrospinal fluid; EYO, estimated years from expected symptom onset; PiB SUVR, Pittsburgh compound B standardized uptake value ratio; SE, standard error.

*Low exercisers reported less than 150 minutes per week of exercise, and high exercisers reported 150 or more minutes of exercise per week.

[†]For consistency with the mutation carrier models (Tables 3 and 4), EYO and family mutation were entered into the mutation noncarrier models.

[‡]The age variable was residualized from EYO.

[§]Adjusted marginal means (SE).

Table 3
Mutation carriers: results from linear models, examining the differences in Pittsburgh compound B positron emission tomography–measured brain amyloid burden and CSF biomarkers between the low and high exercise groups (models also included family mutation, EYO, age, and an EYO*exercise interaction)

	Exercise*					Family mutation			EYO			Age†			EYO*exercise		
	Low exercise	High exercise															
Dependent variable	Mean (SE)‡	Mean (SE)‡	*F*	*P*	η_p^2	*F*	*P*	η_p^2	*F*	*P*	η_p^2	*F*	*P*	η_p^2	*F*	*P*	η_p^2
PiB SUVR (n = 139)	1.59 (0.12)	1.58 (0.09)	2.68	.10	0.020	2.42	.09	0.035	41.30	<.001	0.238	1.86	.17	0.014	3.32	.07	0.025
CSF $A\beta_{42}$ (ng/L) (n = 120)	337.5 (30.7)	349.1 (22.9)	0.01	.95	0.001	1.54	.22	0.026	21.05	<.001	0.157	0.01	.99	0.001	0.04	.85	0.001
CSF tau (ng/L) (n = 121)	81.0 (9.4)	82.1 (6.9)	0.25	.62	0.002	0.85	.43	0.015	13.4	<.001	0.105	0.14	.71	0.001	0.25	.61	0.002

Abbreviations: CSF, cerebrospinal fluid; EYO, estimated years from expected symptom onset; PiB SUVR, Pittsburgh compound B standardized uptake value ratio; SE, standard error.
*Low exercisers reported less than 150 minutes per week of exercise, and high exercisers reported 150 or more minutes of exercise per week.
†The age variable was residualized from EYO.
‡Adjusted marginal means (SE).

APOE ε4 carriage as a covariate and an exercise**APOE* ε4 interaction. Neither the *APOE* ε4 carriage variable nor the interaction term was a significant predictor of brain amyloid in the mutation noncarriers, mutation carrier PiB+, and mutation carrier PiB− groups (data not reported).

3.3. Effect of exercise*EYO interaction on PiB SUVR, CSF $A\beta_{42}$, and CSF tau

On examination of the mutation carrier group as a whole, there was no significant effect of the exercise group*EYO interaction on PiB SUVR (F = 3.32, P = .07), CSF $A\beta_{42}$ (F = 0.04, P = .85), and CSF tau levels (F = 0.25, P = .61; Table 3). After stratification of the mutation carrier group by PiB positivity, an interaction was observed between the exercise group*EYO on PiB SUVR in the PiB+ group (F = 7.04, P = .01, FDR-adjusted P = .03; Table 4, Fig. 2), indicative of a stronger association between brain amyloid and EYO in the low exercisers, compared with the high exercisers. No effect of the exercise*EYO interaction was noted on levels of CSF $A\beta_{42}$ and CSF tau either in the PiB− or PiB+ groups.

4. Discussion

Previous studies of cognitively healthy older adults have established a link between higher physical activity levels and lower levels of AD biomarkers (through PET imaging and CSF biomarker analysis). This study reports, for the first time, an association between higher exercise levels and lower brain amyloid in individuals who have already accumulated high levels of brain amyloid and are carriers of mutations in *APP*, *PSEN1*, or *PSEN2* genes, which are known to cause AD with full penetrance. More specifically, we observed mutation carriers reporting less than 150 minutes of exercise per week had a higher mean level of brain

Table 4
Mutation carriers stratified by brain amyloid load: results from linear models, examining the differences in Pittsburgh compound B positron emission tomography–measured brain amyloid burden and CSF biomarkers between the low and high exercise groups, following stratification of the mutation carriers by PiB PET SUVR status (models also included family mutation, EYO, age, and an EYO*exercise interaction)

	Exercise*					Family mutation			EYO			Age†			EYO*exercise		
	Low exercise	High exercise															
Dependent variable	Mean (SE)‡	Mean (SE)‡	*F*	*P*	η_p^2	*F*	*P*	η_p^2	*F*	*P*	η_p^2	*F*	*P*	η_p^2	*F*	*P*	η_p^2
PiB SUVR																	
MC PiB− (n = 68)	1.09 (0.03)	1.11 (0.02)	1.16	.28	0.019	0.30	.74	0.010	2.27	.14	0.036	0.97	.33	0.016	0.48	.49	0.008
MC PiB+ (n = 71)	2.36 (0.19)	2.16 (0.15)	8.20	.006§	0.114	0.51	.60	0.016	16.22	<.001	0.202	1.92	.17	0.029	7.04	.01§	0.099
CSF $A\beta_{42}$ (ng/L)																	
MC PiB− (n = 57)	387.0 (47.3)	427.8 (31.3)	0.15	.70	0.003	3.02	.06	0.108	1.27	.26	0.025	0.47	.50	0.009	0.00	.99	0.001
MC PiB+ (n = 63)	269.0 (34.9)	290.3 (30.4)	0.34	.56	0.006	0.06	.94	0.002	7.36	.01	0.116	0.38	.54	0.007	0.02	.88	0.001
CSF tau (ng/L)																	
MC PiB− (n = 57)	57.5 (8.6)	64.1 (5.7)	0.01	.98	0.001	0.30	.74	0.012	1.03	.31	0.020	0.15	.70	0.003	0.16	.69	0.003
MC PiB+ (n = 64)	109.9 (16.1)	94.3 (13.4)	0.51	.48	0.009	1.16	.32	0.039	2.22	.14	0.037	1.16	.29	0.020	3.16	.08	0.052

Abbreviations: CSF, cerebrospinal fluid; EYO, estimated years from expected symptom onset; MC, mutation carriers; PiB SUVR, Pittsburgh compound B standardized uptake value ratio; PiB−, PiB negative with an SUVR of less than 1.3; PiB+, PiB positive with an SUVR of 1.3 or higher; SE, standard error.
*Low exercisers reported less than 150 minutes per week of exercise, and high exercisers reported 150 or more minutes of exercise per week.
†The age variable was residualized from EYO.
‡Adjusted marginal means (SE).
§P value remained significant (P < .05) after false discovery rate correction.

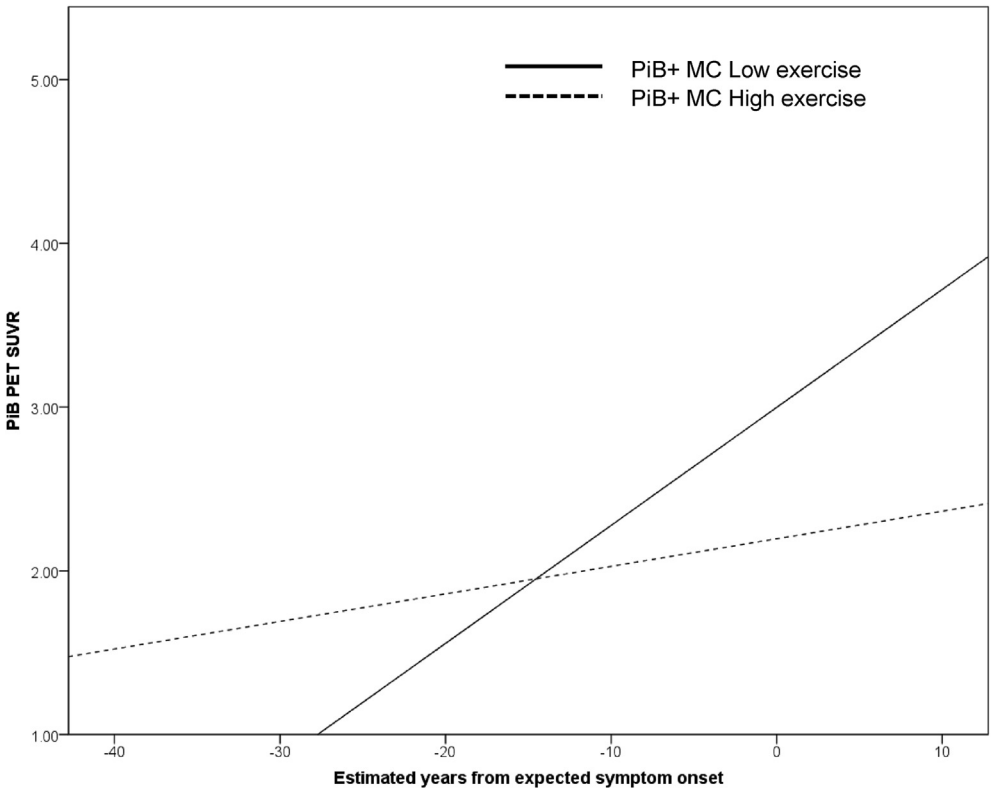

Fig. 2. The association between brain amyloid and EYO is more marked in low exercisers compared with high exercisers. PiB positive (PiB+, i.e., those with an SUVR ≥1.3) mutation carriers (MCs) reporting less than 150 minutes of exercise per week (low exercise) have a more marked association between EYO and Pittsburgh compound B positron emission tomography (PiB PET) standardized uptake value ratio (SUVR) compared with PiB+ MCs reporting more than 150 minutes of exercise per week (high exercise). Abbreviation: EYO, estimated years from expected symptom onset.

amyloid compared with those reporting 150 or more minutes of exercise per week. Furthermore, we report a significant interaction of exercise group*EYO on amyloid load, whereby in PiB+ mutation carrier low exercisers the relationship between brain amyloid and EYO was more marked, compared with high exercisers (Fig. 2).

High levels of physical activity have been previously associated with lower brain amyloid levels in cognitively healthy older adults at increased risk of LOAD because of carriage of a major genetic risk factor (*APOE* ε4 carriage) [17,18]. Consequently, we hypothesized that exercise may also positively influence individuals carrying mutations for ADAD through a reduction in brain Aβ and/or slowed Aβ accumulation. Within the present study, in a cohort of individuals with ADAD genetic mutations who were also dichotomized as PiB+ (i.e., in whom significant levels of aggregated Aβ are already present in the brain), we observed significantly lower levels of cortical amyloid consistent with high levels of exercise. We also observed a significant effect of the interaction term exercise group*EYO on brain amyloid. Our results indicate that in PiB+ low exercisers, the expected strong association between brain amyloid load and EYO exists [2]. Conversely, and importantly, we observed no association between brain amyloid and EYO in the PiB+ high exercisers, which is not the expected course of the disease for individuals with ADAD mutations. Our findings may reflect the notion that low exercisers are more likely to follow the usual disease course of ADAD (i.e., increasing amyloid accumulation with increasing EYO) than high exercisers. Although our findings are novel and promising, the cross-sectional study design does not allow causal inferences. To further examine the relationship between exercise and the trajectory of amyloid accumulation, and subsequent symptom onset in individuals with ADAD mutations, longitudinal analyses of the impact of exercise habits on disease course are vital.

The reported association between exercise and brain amyloid levels was limited to participants who were mutation carriers and PiB+ (i.e., in those with significant pathology present, at levels comparable to a positive PiB scan in sporadic AD). It is possible, however, that the low variability in PiB SUVR levels in those deemed PiB− may account for the lack of findings in this group. Bateman et al. [2] showed Aβ deposition in ADAD mutation carriers begins approximately 20 years before the onset of clinical symptoms. Should exercise be effective in delaying Aβ accumulation, it would be reasonable to assume that this mechanism of action would also be vital in the early stages of neuropathologic changes (i.e., those who are PiB−). Thus, the lack of association in this study between exercise and brain Aβ in the PiB− group is unexpected. To further understand this relationship, a longitudinal study

evaluating exercise levels and brain Aβ over long periods (i.e., from −15 EYO until 0 EYO) is necessary.

In contrast to the observed association between exercise and brain amyloid levels (quantified by PiB PET), we did not observe an association between exercise and CSF levels of $A\beta_{42}$ or tau in the mutation carriers. It is possible that exercise plays a role in reducing the deposition of soluble Aβ into cerebral amyloid plaques, rather than modulating the production of soluble Aβ (levels of which are quantified by the CSF assays). Recent studies have reported a close association between changes in CSF $A\beta_{42}$ and brain amyloid in the earliest stages of AD pathology [26]. Nevertheless, CSF $A\beta_{42}$ levels and brain amyloid levels appear to diverge once significant plaque load is present; which may explain the lack of association between CSF $A\beta_{42}$ and exercise levels in the PiB+ group. The use of amyloid brain imaging may provide a more robust measurement for the evaluation of the relationship between exercise and aggregation of Aβ into amyloid plaques. However, because of the vast literature supporting the use of CSF Aβ42 and tau as biomarkers of AD [27], these measurements should be considered in future longitudinal studies of exercise and AD biomarkers.

We report an association between exercise levels and brain amyloid in those with genetic mutations known to cause increased Aβ; nevertheless, whether exercise is associated with reduced Aβ deposition or enhanced Aβ clearance remains to be established. Aβ is produced from the APP, which is cleaved via one of two competing pathways: the nonamyloidogenic pathway and the amyloidogenic pathway [28]. Evidence from animal studies indicates exercise may contribute to both the alteration of APP processing toward the nonamyloidogenic pathway resulting in reduced Aβ production *and* to improvement of Aβ clearance in the brain. Indeed, decreased levels of APP cleavage fragments (αCTFs and βCTFs), but not levels of APP itself, have been observed in exercising AD transgenic mice, suggesting increased nonamyloidogenic processing [9,11]. Furthermore, exercise-induced increases in activity of neprilysin and insulin-degrading enzyme, both known Aβ proteases, indicate a positive effect of exercise on Aβ degradation [29,30]. It is possible that through the conduct of both longitudinal studies and well-designed exercise intervention trials, we may have the opportunity to establish whether exercise contributes to decreased Aβ deposition or enhanced clearance (or possibly both), in this unique cohort of individuals carrying ADAD genetic mutations.

To our knowledge, this preliminary study is the first report of an association between exercise level and brain amyloid in a cohort of presymptomatic ADAD mutation carriers. Nevertheless, this study is not without limitations. As stated earlier, this is a cross-sectional analysis, and thus the direction of the reported associations cannot be inferred. Although it is possible that low exercise might be an early symptom of amyloid accumulation, the association between exercise and amyloid remained stable following adjustment for EYO. A more likely hypothesis is that higher exercise alters amyloid accumulation, which is supported by previous animal work; however, this hypothesis requires further investigation using longitudinal and intervention trial designs. Furthermore, we used an exercise questionnaire specifically designed for this study (i.e., not previously validated) and also acknowledge that the reported exercise levels are higher than that of the wider community. Nevertheless, it is likely that our cohort is highly motivated to participate in exercise, given the increasing literature linking a healthy lifestyle (including exercise) to reduced biomarkers of AD, and enhanced overall cognitive health. Coupled with corroboration of reports by a collateral source and truncation of exceptionally high reports, we believe the reports of exercise are a relatively true representation in this unique genetic group. It is important to note that we only quantified the duration of exercise undertaken by participants. Future studies should evaluate intensity, frequency, duration, and type of exercise and physical activities, in an attempt to identify the optimum exercise/physical activity regimen, in terms of modulating AD biomarkers. We attempted to control for factors, which may confound the relationship between exercise and AD pathology, including EYO, age, and *APOE* ε4 allele carriage. Nonetheless, we were limited by a small sample size, which thus requires limited inclusion of additional variables of interest in the model. Importantly, exercise may be a proxy for other healthy lifestyle decisions and behaviors, including dietary habits, midlife obesity, body mass index, and tobacco abuse, among other potential modifiable risk factors shown to modify AD risk and pathology in non-ADAD cohorts.

To our knowledge, this study is the first to demonstrate an association between high levels of exercise and lower brain amyloid as a function of estimated years from expected symptom onset in those known to have ADAD genetic mutations and in whom high levels of brain amyloid are already present. These findings support previous work conducted in cognitively healthy older adults; however, the relationship between brain amyloid and exercise in ADAD mutation carriers requires further confirmation. Future research should include longitudinal studies of exercise and brain amyloid levels to inform intervention trials with amyloid as the primary outcome measure.

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Author Contributions: B.M.B. completed the literature search and prepared the figures. B.M.B. and R.N.M. designed this substudy; R.J.B. and J.C.M. designed larger DIAN study. All the authors with the DIAN collected the data. B.M.B. and C.X. conducted the analysis. B.M.B., R.N.M., J.J.P., S.R.R-S., and K.I.E. interpreted the data and wrote the report. All coauthors critically reviewed the report.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed previous literature via usual methods (e.g., PubMed). Previous cross-sectional observational studies have demonstrated an association between higher physical activity levels and lower cerebral amyloid load. This relationship has also been reported to be more prominent in carriers of the apolipoprotein E ε4 allele, the greatest known genetic risk factor for late-onset sporadic Alzheimer's disease (AD).
2. Interpretation: This study used data from mutation carriers of autosomal dominant AD genes, which are known to cause AD with full penetrance at an early age (usually less than 50 years). By studying this unique cohort of individuals, we are able to evaluate the relationship between self-reported exercise levels and markers of AD pathology, in those we know will develop the condition at a young age. We report a relationship between self-reported exercise levels and cerebral amyloid load in mutation carriers already accumulating AD pathology, as a function of their estimated years from expected symptom onset.
3. Future directions: Although numerous studies, including the present study, have demonstrated a cross-sectional relationship between physical activity levels and cerebral amyloid load, this evidence requires further validation in longitudinal and intervention studies.

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