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Relationship between physical activity, cognition, and Alzheimer pathology in autosomal dominant Alzheimer's disease

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Abstract

Introduction: Little is known about effects of physical activity (PA) in genetically driven early-onset autosomal dominant Alzheimer's disease (AD).

Methods: A total of 372 individuals participating at the Dominantly Inherited Alzheimer Network study were examined to evaluate the cross-sectional relationship of PA with cognitive performance, functional status, cognitive decline, and AD biomarkers in cerebrospinal fluid. Mutation carriers were categorized as high or low exercisers according to WHO recommendations.

Results: Mutation carriers with high PA showed significantly better cognitive and functional performance and significantly less AD-like pathology in cerebrospinal fluid than individuals with low PA. Mutation carriers with high PA scored 3.4 points better on Mini Mental State Examination at expected symptom onset and fulfilled the diagnosis of very mild dementia 15.1 years later compared with low exercisers.

Discussion: These results support a beneficial effect of PA on cognition and AD pathology even in individuals with genetically driven autosomal dominant AD.

Keywords

Physical activity; Dominantly inherited Alzheimer's disease; Cognitive function; Functional status; Cerebrospinal fluid biomarkers; Mutation carrier

1. Background

Previous reports suggest that physical activity (PA) has beneficial effects on cognitive function in healthy elderly people, individuals at risk of Alzheimer's disease (AD) (i.e., individuals with mild cognitive impairment), and in persons with dementia (including dementia due to AD) [1–5]. In addition, PA has shown beneficial effects on the rate of cognitive decline in healthy elderly individuals with mild cognitive impairment or mild dementia due to AD [2,5–10]. Furthermore, PA has been shown to lower the risk of AD [11–15]. In line with these findings, PA appears to slow the neuropathological changes associated with AD [16–19]. Given these beneficial effects of PA on cognitive function and cognitive decline [20], a new guideline recommends regular physical exercise for people with mild cognitive impairment (level B) [21].

In the present study, we examined asymptomatic and symptomatic autosomal dominant Alzheimer's disease (ADAD) family members participating in the Dominantly Inherited Alzheimer Network (DIAN) [22]. Autosomal dominant AD is a rare form of AD resulting in aggregation of the amyloid- β peptide into amyloid plaques due to alteration of amyloid- β processing. In the present study, we aimed to determine if current recommendations from World Health Organization and the American College of Sports Medicine [23,24] of at least 150 minutes of PA per week (min/week) may have beneficial effects on global cognition, cognitive decline, functional status, and AD biomarkers in the brain and cerebrospinal fluid (CSF) in ADAD.

2. Methods

2.1. Participants

Information regarding participant enrollment and procedures of the DIAN study has previously been described in detail [22]. Briefly, DIAN Study is a longitudinal observational study recruiting participants at risk for known mutations in one the abovementioned three genes. Participants undergo clinical, neuropsychological, imaging, blood, and CSF biomarkers analyses [22,25].

From data release of DIAN DF-11 (June 7, 2017), a total of 459 (noncarriers = 184 and mutation carriers = 275) participants had baseline data. Individuals with missing clinical, exercise, CSF, and/or PET data were excluded from the analysis (see Table 1 for full description of participant numbers). Table 1 summarizes the demographic and clinical characteristics of each clinical group.

All aspects of the study have been approved by the institutional review boards for each of the participating sites in the DIAN study. Experimental protocols described in the present study have been approved by the Ethik Kommission an der Medizinischen Fakultät der Eberhard-Karls-Universität und am Universitätsklinikum Tübingen. All participants provided written informed consent.

2.2 . Clinical assessments

Participants underwent clinical assessment of cognitive and functional performance using the Clinical Dementia Rating (CDR) scale consisting of six domains including memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. The CDR yields a global and a Sum of Boxes (SOB) score. The CDR global score ranges from 0 (i.e., normal/asymptomatic state) to 3 (i.e., severe dementia) at ordinal scales level [26]. The CDR-SOB score ranges from 0 (i.e., normal/asymptomatic state) to 18 (i.e., severe dementia) at metric scales level and has been considered to stage patients in the course of AD in more detail than the global score [27]. A CDR-SOB score of 3.0 to 4.0 indicates very mild dementia [27]. Participants also completed the Mini Mental State Examination (MMSE) at baseline [28].

Estimated years to symptom onset (EYO) were calculated as the age of the participants at baseline assessment minus the age of their parents or first-degree relative at symptom onset as previously described [25,29]. For example, if the participant's age was 37 years and the parent's or first-degree relative's age at onset was 45 years, then the estimated years to expected symptom onset would be 8. As all participants of the DIAN study are members of affected ADAD families, the construct of EYO can be applied to both mutation carriers and noncarriers, resulting in age-matched cases and controls. The EYO concept allows the use of cross-sectional data to gain insight into the disease trajectory over time and has been validated in the DIAN study as providing a highly accurate estimate of AD biomarkers staging and symptom onset [25,29].

2.3. Exercise level evaluation

Information about the average time spent partaking in ten various leisure-time exercise activities (e.g., walking, running, cycling, swimming, tennis, aerobics, or weight training) over the past 12 months was given by the participants via questionnaire, corroborated by their collateral source (e.g., family member or friend). A continuous score (i.e., minutes per week) was calculated from all items by the addition of minutes per week spent exercising in each activity. Outliers were minimized by truncation of individual item responses to a maximum of 600 minutes (following similar guidelines of maximum daily activities of those recommended for the International Physical Activity Questionnaire [30]). We stratified this continuous score based on current recommendations from the World Health Organization and the American College of Sports Medicine of a minimum of 150 minutes PA per week [23,24]. Mutation carriers reporting less than 150 minutes of PA per week were categorized into a low-PA group (n = 68), and those mutation carriers participating in more than or equal to 150 minutes of activity per week were categorized into a high-PA group (n = 156).

2.4. Measurement of AD-related biomarkers in CSF and in the brain

CSF concentrations of amyloid- β_{1-42} , total tau, and phosphorylated tau₁₈₁ (at threonine 181) were measured by Luminex-based immunoassay (AlzBio3; Fujirebio, Ghent, Belgium). Images obtained through PET with the use of Pittsburgh compound B (Pittsburgh compound B-PET) were coregistered with individual magnetic resonance imaging images for region-of-interest determination. For each region of interest (FreeSurfer defined, MA), the standardized uptake value ratio (SUVR) was calculated with the cerebellar cortex used as

the reference region. The SUVR of the prefrontal cortex, temporal lobe, gyrus rectus, and precuneus were averaged to calculate a total cortex SUVR. An increased Pittsburgh compound B SUVR indicates increased binding to fibrillar amyloid [25,31].

2.5. Statistical analysis

All statistical analyses were conducted using JMP®, version 13.1.0 (SAS Institute Inc., Cary, NC; 1989–2016). Differences in clinical characteristics and cognitive, biochemical, and imaging parameters between noncarriers and mutation carriers as well as between mutation carriers with high- versus low-PA status were tested using parametric analyses (independent sample *t*-tests) or nonparametric analyses (Pearson Chi-square, Mann-Whitney U) when appropriate. A *P* value of .05 (2-sided) or smaller determined a significant result. Values for individual participants are not displayed on graphs (i.e., as a scatter plot) to protect the confidentiality of the mutation status of participants (e.g., based on EYO alone, a participant could potentially deduce their mutation status). Regression analyses were adjusted for potential confounders including age, gender, depression, and education.

PA differences between mutation carriers and noncarriers with respect to EYO were assessed by using a covariate-adjusted linear regression model with PA (min/week) as dependent variable and EYO and group (i.e., noncarriers and mutation carriers) as independent variables with the inclusion of a group*EYO interaction.

Differences in baseline global cognition (MMSE score) or functional status (CDR-SOB) between mutation carriers and noncarriers as a function of PA (min/week) were calculated by running covariate-adjusted linear regression models with MMSE or CDR-SOB as dependent variables and PA (min/week) and group (i.e. noncarriers and mutation carriers) as independent variables with the inclusion of a group*PA interaction term. Likewise, a polynomial regression model with PA as a quadratic term was introduced to evaluate a possible dose-response relationship of PA on MMSE or CDR-SOB.

In a next step, we evaluated if mutation carriers with either high or low PA differed in MMSE and CDR-SOB scores with respect to EYO. For this cross-sectional analysis, a covariate-adjusted linear regression model with MMSE or CDR-SOB as dependent variable and EYO and PA group (i.e., high vs. low) as independent variables with the inclusion of a PA group*EYO interaction was conducted.

To evaluate differences in AD biomarkers (i.e., CSF levels of amyloid- β_{1-42} , total tau, phosphorylated tau₁₈₁, the ratios of total tau/amyloid- β_{1-42} , phosphorylated tau/ amyloid- β_{1-42} , as well as brain amyloid burden) between mutation carriers with high or low PA with respect to EYO, we conducted a series of linear regression models. AD biomarkers were introduced as dependent variables and EYO and activity group (i.e., high vs. low) as independent variables with the inclusion of a group*EYO interaction term.

3. Results

3.1. Demographics and clinical parameters in mutation carriers and noncarriers of the DIAN study

Baseline demographics; clinical characteristics; and cognitive, biochemical, and imaging parameters in mutation carriers and noncarriers are displayed in Table 1. At baseline, no differences in age, EYO, gender, years of education, and duration of PA per week were observed between mutation carriers and noncarriers.

3.2. Association between PA and EYO in mutation carriers and noncarriers

Interestingly, the level of PA was comparable between mutation carriers (314.2 min/week) and noncarriers (297.2 min/week) showing no significant difference ($P = .441$) (Table 1). However, when considering the level of PA in mutation carriers and noncarriers along EYO, we found a significant group*EYO interaction ($F_{[1,368]} = 9.018$; $P = .0029$). This effect was mostly driven by a significant decrease of PA duration in mutation carriers over time (EYO) ($\beta = -4.915$; 95% confidence interval [CI], -7.875 to -1.955 ; $P = .0012$), whereas noncarriers showed no significant association between PA duration and EYO ($\beta = 1.316$; 95% CI, -1.460 to 4.093 ; $P = .351$).

3.3. Association between MMSE score/CDR-SOB score and PA in mutation carriers and noncarriers

There was a relatively high trend for a group*PA interaction ($F_{[1,364]} = 5.070$; $P = .0593$) indicating that MMSE performance was dependent on mutation status and PA. In mutation carriers, an increase in PA was accompanied by higher MMSE scores (i.e., better global cognition; $\beta = 0.0039$; 95% CI, 0.0013 to 0.0067 ; $P = .004$). However, this association was slightly better explained by a quadratic term ($b = 0.0044$; 95% CI, 0.0018 to 0.0071 ; $P = .0011$) indicating a dose-response relationship of PA on MMSE in mutation carriers (Fig. 1A). In contrast, in noncarriers, global cognition seems not to be influenced by PA as there was neither a significant linear association ($P = .862$) nor a quadratic relationship ($P = .657$) between PA duration and MMSE performance (Fig. 1A).

CDR-SOB performance was significantly influenced by mutation status and PA ($F_{[1,364]} = 5.578$; $P = .0249$). In mutation carriers, lower CDR-SOB (i.e., minor impairment) was significantly associated with an increase in PA ($\beta = -0.002$; 95% CI, -0.004 to -0.0009 ; $P = .0015$). Similarly, we found a dose-response relationship of PA on CDR-SOB (Fig. 1B) as this association was slightly better explained by a quadratic term ($\beta = -0.002$; 95% CI, -0.004 to -0.001 ; $P = .0007$). In noncarriers, there was neither a linear association ($P = .665$) nor a quadratic relationship ($P = .839$) between PA and CDR-SOB performance observable.

3.4. Demographics, clinical parameters, and AD biomarkers in mutation carriers with high or low PA

Baseline demographics; clinical characteristics; and cognitive, biochemical, and imaging parameters in mutation carriers with high versus low PA are displayed in Table 2. Interestingly, mutation carriers with high PA performed better on MMSE (Fig. 2A; 28.2

± 2.5 points vs. 25.1 ± 6.4 points; $P < .0001$) and CDR-SOB (Fig. 2B; 0.7 ± 1.4 points vs. 2.0 ± 3.2 points; $P < .0001$) than mutation carriers with low PA. In addition, mutation carriers with high PA exhibited lower baseline levels of CSF total tau (103.7 ± 67.1 pg/mL vs. 1443.3 ± 106.9 pg/mL; $P = .0019$) and phosphorylated tau₁₈₁ (60.8 ± 35.6 pg/mL vs. 72.2 ± 42.0 pg/mL; $P = .0296$), lower ratios of CSF total tau/amyloid- β_{1-42} (0.25 ± 0.2 vs. 0.43 ± 0.4 ; $P = .0002$) and phosphorylated tau/amyloid- β_{1-42} (0.15 ± 0.2 vs. 0.21 ± 0.1 ; $P < .0146$), and higher levels of CSF amyloid- β_{1-42} (581.5 ± 305.2 pg/mL vs. 470.6 ± 259.2 pg/mL; $P = .0178$) than mutation carriers with low PA (Fig. 3).

3.5. Association between MMSE score/CDR-SOB score and EYO in mutation carriers with high or low PA

Differences in MMSE scores were significantly influenced by PA status (i.e., high vs. low) and EYO (PA status*EYO: $F_{[1,221]} = 8.906$; $P = .0032$; Fig. 2C). Mutation carriers in the low-PA group revealed greater decline on MMSE scores with respect to EYO ($\beta = -0.251$; 95% CI, -0.409 to -0.0924 ; $P = .0024$) than mutation carriers with high PA ($\beta = -0.102$; 95% CI, -0.139 to -0.065 ; $P < .0001$). Mutation carriers with high PA are estimated to score 3.4 points better on MMSE (26.9 ± 2.1 points) at expected symptom onset (i.e., EYO = 0) than mutation carriers with low PA (MMSE: 23.5 ± 3.2 points; Fig. 5A).

CDR-SOB outcome was significantly influenced by PA status (i.e., high vs. low) and EYO (PA status*EYO: $F_{[1,221]} = 5.226$; $P = .0233$; Fig. 2D). Mutation carriers in the low-PA group revealed greater increase on CDR-SOB with respect to EYO ($\beta = 0.158$; 95% CI, 0.082 to 0.234 ; $P = .001$) than mutation carriers with high PA ($\beta = 0.089$; 95% CI, 0.069 to 0.111 ; $P < .0001$). Mutation carriers with high PA reveal a CDR-SOB score of 3.0 (i.e., very mild dementia) 15.1 years later (i.e., at EYO = 16.2) compared with mutation carriers with low PA (i.e., at EYO = 1.1; Fig. 5B).

3.6. Association between AD biomarkers and EYO in mutation carriers with high or low PA

Significant differences in CSF levels of total tau in relation to PA status (i.e., mutation carriers with high or low PA) and EYO have been detected (PA status*EYO: $F_{[1,185]} = 3.963$; $P = .0480$; Fig. 4). An increase in CSF levels of total tau was more pronounced in mutation carriers with low activity status with respect to EYO ($\beta = 4.404$; 95% CI, 1.594 to 7.216 ; $P = .0009$) than that in mutation carriers with high PA ($\beta = 3.437$; 95% CI, 2.341 to 4.532 ; $P < .0001$).

In addition, ratios of total tau/amyloid- β_{1-42} increased in mutation carriers with low-PA status with respect to EYO ($\beta = 0.024$; 95% CI, 0.014 to 0.033 ; $P < .0001$) compared with those in mutation carriers with high PA ($\beta = 0.0138$; 95% CI, 0.009 to 0.0176 ; $P < .0001$) as indicated by a significant PA status*EYO interaction ($F_{[1,185]} = 5.164$; $P = .0244$; Fig. 4).

For CSF levels of phosphorylated tau₁₈₁ ($F_{[1,185]} = 1.612$; $P = .206$), amyloid- β_{1-42} ($F_{[1,185]} = 0.021$; $P = .973$), phos-phorylated tau/amyloid- β_{1-42} ratio ($F_{[1,185]} = 1.652$; $P = .203$), and global amyloid- β brain burden ($F_{[1,185]} = 0.261$; $P = .611$), there were no significant interaction effects (Fig. 4).

4. Discussion

In this study, we have extensively examined the impact of PA on global cognition, functional status, and CSF biomarkers of AD in a unique population of well-characterized individuals with ADAD participating in the DIAN study.

Our cross-sectional data showed that mutation carriers reporting less than 150 minutes of PA per week had poorer global cognition and greater decline in global cognition with respect to EYO than those reporting 150 or more minutes of PA per week even after controlling for age. These results are in line with previous studies demonstrating beneficial effects of PA on cognitive function, cognitive preservation, and cognitive decline in elderly people[11,15,20,32–36].

By modeling the trajectory of cognitive and functional differences (i.e., MMSE and CDR-SOB against EYO) we observed a lower level of cognitive and functional impairment in participants with high PA. In particular, we found that at expected symptom onset (i.e., EYO = 0), mutation carriers with high PA (i.e., exercise duration ≥ 150 min/week) scored 3.4 points better on MMSE, had a 1.3 points lower CDR-SOB score, and revealed a CDR-SOB score of 3.0 (i.e., very mild dementia) 15.1 years later than mutation carriers with low PA (i.e., exercise duration < 150 min/week). Thus, the duration of PA seems to be a powerful modulator of cognitive performance and the rate of cognitive decline even in participants with genetically driven ADAD.

In our study, the relationship between PA and cognitive performance as well as functional status followed a dose-response curve. A duration of ≥ 150 minutes per week of PA was significantly associated with better cognition and functional status in the study population. This result strengthens the current recommendations from WHO and the American College of Sports Medicine [23,24] that performing at least 150 minutes per week of PA is required to obtain beneficial effects on cognitive functioning and delaying cognitive decline. Although PA levels in mutation carriers were comparable to those in noncarriers at baseline and decreased along EYO, 70% of our examined mutation-carrier population achieved the recommended amount of at least 150-min PA per week. In a next step, we examined the relationship between PA and biomarkers of AD. We found that mutation carriers in the high-exercise group exhibited lower baseline levels of CSF total tau and phosphorylated tau₁₈₁, higher levels of CSF amyloid- β_{1-42} , lower ratios of CSF total tau/amyloid- β_{1-42} , and lower global amyloid- β brain burden than mutation carriers with low-PA status. Thus, even after controlling for age, mutation carriers with high PA levels exhibited lower AD-like pathology in CSF and in the brain than mutation carriers with low-PA levels. In addition, mutation carriers with high PA showed a shift of the cross-sectionally estimated trajectories of CSF levels of total tau and total tau/amyloid- β_{1-42} ratio to the left, that is, to less progressed levels of AD pathology. These results are in line with previous studies demonstrating that higher levels of self-reported PA have been associated with lower levels of brain amyloid and with increased CSF levels of amyloid- β_{1-42} in late-onset AD patients [16,18,19]. Furthermore, studies with animal models of AD revealed positive effects of exercise on underlying mechanisms of amyloid- β and/or tau aggregation in AD transgenic mice [37–43]. However, our results are in contrast with recently published findings in presymptomatic

mutation carriers of ADAD, in which the authors found no differences in brain amyloid load, CSF amyloid- β_{1-42} , or CSF tau levels between low- and high-exercise mutation carriers [44]. This discrepancy may be due to a different mutation carrier population (preclinical and clinical mutation carriers in our study vs. only preclinical mutation carriers in the study by Brown et al. [44]) and sample size (224 mutation carriers in our study vs. 139 mutation carriers in the study by Brown et al. [44]) between both the studies.

With respect to interpretation of the results, potential limitations of this study should be taken into consideration. First, we examined only cross-sectional data. Thus, individual trajectories of cognitive changes could not be assessed in the present study. However, the trajectories assessed across the spectrum of AD severity at the cross-sectional level provide an acceptable proxy of the expected trajectories when assessed longitudinally, which awaits further validation once sufficient longitudinal data become available in the DIAN study. Second, the low-PA group was older and was cognitively more impaired at baseline than the high-PA group. Third, both directions of causality are plausible (exercise strongly protects against clinical impairment and/or advancing dementia diminishes exercise). Fourth, we focused our analyses on the MMSE and CDR-SOB scores. Future studies may use a wider spectrum of neuropsychological tests to capture global cognitive and memory abilities in a more comprehensive manner. In addition, the self-reported questionnaire used in the DIAN study, while corroborated by an informed project partner, does not capture all the details of the daily PA and has not been confirmed by objective measures (e.g., actigraphy). At last, the intensity of PA modalities was not assessed in the present study.

In conclusion, the findings reported here show a significant relationship between PA, cognition and functional status, and AD pathology even in individuals with genetically driven ADAD. The relationship between PA and cognitive performance followed a dose-response curve. The officially recommended PA duration of 150 minutes per week was associated with significantly better cognition and less AD pathology in ADAD. From a public health perspective, this amount of PA was achieved by 70% of all ADAD individuals participating at the DIAN study. Therefore, a physically active lifestyle is achievable and may play an important role in delaying the development and progression of ADAD. Individuals at genetic risk for dementia should therefore be counseled to pursue a physically active lifestyle.

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RESRESEARCH IN CONTEXT

1. Systematic review: We searched PubMed for articles with the terms “Dominantly Inherited Alzheimer Network”, “Alzheimer’s disease”, “physical activity”, “cognition”, and “biomarkers”. Although numerous reports suggest that physical activity (PA) may have beneficial effects on cognition and pathological changes associated with late-onset Alzheimer’s disease (AD), none of the reviewed studies directly examined the impact of PA on cognition and functional performance in patients with autosomal dominant AD.
2. Interpretation: Our results are the first, supporting a beneficial effect of PA on cognition and dementia signs and symptoms in individuals with genetically driven autosomal dominant AD. Higher PA is associated with less AD-like pathology in CSF, leads to better cognitive outcome at expected symptom onset, and delays the diagnosis of very mild dementia.
3. Future directions: A physically active lifestyle seems to play an important role in slowing the development and progression of autosomal dominant AD.

Fig. 1.

(A) Global cognitive function as assessed by the Mini Mental State Examination (MMSE) score in mutation carriers and noncarriers with respect to time spent in leisure-time exercise activities. The quadratic model fit lines are presented in blue for noncarriers and red for mutation carriers. (B) Functional and cognitive performance as assessed by the Clinical Dementia Rating scale-Sum of Boxes (CDR-SOB) in mutation carriers and noncarriers with respect to time spent in leisure-time exercise activities. The quadratic model fit lines are presented in blue for noncarriers and red for mutation carriers. Abbreviations: MCs, mutation carriers; NCs, noncarriers.

Fig. 2.

(A) Baseline levels of global cognitive function as assessed by the Mini Mental State Examination (MMSE) score in mutation carriers with either high (i.e., ≥ 150 min/week) or low (i.e., <150 min/week) physical activity. (B) Baseline levels of Clinical Dementia Rating scale-Sum of Boxes (CDR-SOB) in mutation carriers with either high or low physical activity. (C) MMSE as a function of estimated years to expected symptom onset (EYO) in mutation carriers with either high-physical activity or low-physical activity status. The regression lines are presented in red for the high-physical activity group and blue for the low-physical activity group. (D) CDR-SOB as a function of EYO in mutation carriers with either high or low physical activity. The regression lines are presented in red for the high-physical activity group and blue for the low-physical activity group.

Fig. 3.

Baseline levels of Alzheimer's disease biomarkers (i.e., global Pittsburgh compound B [PIB] uptake, CSF levels of amyloid- β_{1-42} ($A\beta_{1-42}$), total tau (ttau), phosphorylated tau181 (p-tau₁₈₁), as well as t-tau/ $A\beta_{1-42}$ and p-tau₁₈₁/ $A\beta_{1-42}$ ratio) in mutation carriers with either high (i.e., ≥ 150 min/week) or low (i.e., <150 min/week) physical activity status.

Fig. 4.

Alzheimer's disease biomarkers (i.e., global Pittsburgh compound B [PIB] uptake, CSF levels of amyloid- $A\beta_{1-42}$ ($A\beta_{1-42}$), total tau (t-tau), phosphorylated tau₈₁ (p-tau₁₈₁), as well as t-tau/ $A\beta_{1-42}$ and p-tau₁₈₁/ $A\beta_{1-42}$ ratio) as a function of estimated years to expected symptom onset (EYO) in mutation carriers with either high (i.e., 150 min/week) or low (i.e., <150 min/week) physical activity status. The regression lines are presented in red for the high-physical activity group and blue for the low-physical activity group.

Fig. 5.

(A) Estimated difference in global cognitive function as assessed by the Mini Mental State Examination score (MMSE) in mutation carriers with either high (i.e., ≥ 150 min/week) or low (i.e., <150 min/week) physical activity at expected symptom onset (i.e., EYO = 0). Mutation carriers with high-physical activity score 3.4 points better on MMSE evaluation than mutation carriers with low physical activity at expected symptom onset. The dotted line in red reflects MMSE score of the high-physical activity group (26.9 ± 2.1 points) and in blue for the low-physical activity group (23.5 ± 3.2 points) at EYO = 0. (B) Estimated difference in years matching the diagnosis of very mild dementia according to Clinical Dementia Rating scale-Sum of Boxes (CDR-SOB) in mutation carriers with either high or low physical activity. Mutation carriers with high physical activity reveal a CDR-SOB score of 3.0 (i.e., very mild dementia) 15.1 years later compared with mutation carriers with low physical activity. The dotted line in red reflects EYO of the high-physical activity group (EYO = 16.2) and in blue for the low-physical activity group (EYO = 1.1) when both the groups match the criteria of very mild dementia according to CDR-SOB.

Table 1

Baseline demographics; clinical characteristics; and cognitive, biochemical, and imaging parameters in mutation carriers and noncarriers

Baseline characteristics	Mutation carriers* (n = 224)	Noncarriers (n = 148)	P value
Age (years)	38.4 (9.9)	38.8 (10.4)	.696
Estimated years to symptom onset	-8.3 (9.4)	-8.2 (11.5)	.913
Gender (females, %)	124 (55)	88 (59)	.434
Education (years)	13.0 (3.2)	14.5 (2.9)	.103
Geriatric Depression Scale	2.5 (2.8)	1.6 (1.9)	.0005
MMSE	27.2 (4.5)	29.0 (1.3)	<.0001
CDR global score	0.2 (0.3)	0.00 (0.0)	<.0001
CDR-SOB	1.9 (3.2)	0.01 (0.3)	<.0001
Physical activity (min/week)	314.2 (216.7)	297.2 (194.5)	.441
Global PIB-uptake	1.43 (0.4)	1.06 (0.1)	<.0001
CSF amyloid- β_{1-42} (pg/mL)	547.9 (295.8)	789.7 (287.8)	<.0001
CSF t-tau (pg/mL)	116.0 (83.1)	58.4 (26.5)	<.0001
CSF p-tau ₁₈₁ (pg/mL)	64.3 (37.9)	29.5 (10.5)	<.0001
t-tau/amyloid- β_{1-42} ratio	0.31 (0.3)	0.08 (0.03)	<.0001
p-tau/amyloid- β_{1-42} ratio	0.16 (0.1)	0.04 (0.02)	<.0001

Abbreviations: APP, amyloid precursor protein; CDR, Clinical Dementia Rating scale; Global PIB-uptake, global cerebral amyloid- β burden as measured by ^{11}C -PittsburghCompound-B PET; MMSE, Mini Mental State Examination; PSEN1, Presenilin 1; PSEN2, Presenilin2; p-tau, phosphorylatedtau; SD, standard deviation; SOB, Sum of Boxes; t-tau, total tau.

NOTE. Data are given as mean (SD) or number (%). Significant differences are in bold.

* Thereof, n = 165 are PSEN1 mutation carriers, n = 20 are PSEN2 mutation carriers, and n = 39 are APP mutation carriers.

Table 2

Baseline demographics; clinical characteristics; cognitive, biochemical, and imaging parameters in mutation carriers with high (i.e., 150 min/week) or low (i.e., <150 min/week) physical activity

Baseline characteristics	High-active mutation carriers (n = 156)	Low-active mutation carriers (n = 68)	P value
Age (years)	37.3 (10.2)	41.1 (8.9)	.0084
Estimated years till symptom onset	-9.6 (8.4)	- 5.3 (8.2)	.0012
Gender (females, %)	84 (54%)	42 (62%)	.272
Education (years)	14.1 (3.1)	13.8 (3.3)	.496
Geriatric Depression Scale	2.1 (2.6)	2.5 (2.6)	.252
MMSE	28.2 (2.5)	25.1 (6.4)	<.0001
CDR global score	0.2 (0.3)	0.4 (0.4)	.0002
CDR-SOB	0.7 (1.4)	2.0 (3.2)	<.0001
Physical activity (min/week)	425.5 (159.2)	58.9 (52.4)	<.0001
Global PIB-uptake	1.39 (0.3)	1.52 (0.5)	.0539
CSF amyloid- β_{1-42} (pg/mL)	581.5 (305.2)	470.6 (259.2)	.0178
CSF t-tau (pg/mL)	103.7 (67.1)	144.3 (106.9)	.0019
CSF p-tau ₁₈₁ (pg/mL)	60.8 (35.6)	72.2 (42.0)	.0296
t-tau/amyloid- β_{1-42} ratio	0.25 (0.2)	0.43 (0.4)	.0002
p-tau/amyloid- β_{1-42} ratio	0.15 (0.1)	0.21 (0.2)	.0146

Abbreviations: CDR, Clinical Dementia Rating scale; Global t-tau, total tau; MMSE, Mini Mental State Examination; PIB-uptake, global cerebral amyloid-b burden as measured by ¹¹C-Pittsburgh Compound-B PET; p-tau, phosphorylated tau; SOB, Sum of Boxes.

NOTE. Data are given as mean (SD) or number (%). Significant differences are in bold.

NOTE. Mutation carriers with high physical activity reported 150 or more minutes of exercise per week, and mutation carriers with low physical activity reported less than 150 minutes per week of exercise.