Physical activity, cognition, and Alzheimer pathology in autosomal dominant Alzheimer`s disease

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Abstract

Background: Previous reports suggest that physical activity (PA) may have beneficial effects on cognitive function, cognitive decline and Alzheimer`s disease (AD) risk in elderly people. In addition, PA may modify pathological changes associated with AD. However, the effects of PA on cognitive performance and AD biomarkers in cerebrospinal fluid (CSF) in autosomal dominant Alzheimer`s disease (ADAD) are unknown and have considerable relevance regarding interventions to retard disease onset.

Methods: A total of 372 individuals (224 mutation carriers [MCs] and 148 non-carriers [NCs]) participating at the Dominantly Inherited Alzheimer Network (DIAN) study were examined to evaluate the cross-sectional relationship between PA and cognitive performance, functional status, cognitive decline and AD biomarkers in CSF. MCs were categorized into those with high PA (≥150 minutes/week) vs. those with low PA (<150 minutes/week).

Findings: MCs with high PA showed significantly better cognitive and functional performance at baseline and with respect to estimated years from expected symptom onset (EYO) compared to individuals with low PA. In addition, MCs with high PA demonstrated significantly less AD-like pathology in CSF compared to individuals with low PA. MCs with high PA scored 3·4 points better on MMSE evaluation at expected symptom onset and fulfilled the diagnosis of very mild dementia 15·1 years later compared to MCs with low PA.

Interpretation: These results are supportive of a beneficial effect of PA on cognition and AD pathology even in individuals with genetically driven ADAD. However, both directions of causality are plausible (exercise strongly protects against clinical impairment and/or advancing dementia diminishes exercise). A physically active lifestyle may play an important role in slowing the development and progression of ADAD.

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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 [MCI]) 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 MCI or mild 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 MCI (Level B).[21]

However, the majority of studies examining the relationship between PA, cognitive function and AD biomarkers were conducted with older adults. According to current knowledge, sporadic late onset AD (LOAD) and autosomal-dominant AD (ADAD) show amyloid accumulation up to two decades prior to the presentation of clinical symptoms.[22,23] Thus, there is a need to examine the effects of PA on biomarkers of AD at early stages. For that reason, the present study examined asymptomatic and symptomatic ADAD family members participating in the Dominantly Inherited Alzheimer Network (DIAN).[24] ADAD is a rare form of AD resulting in aggregation of the amyloid-β (Aβ) peptide into amyloid plaques due to alteration of Aβ processing. Mutation carriers (MCs) of ADAD develop the disease typically at a younger age than individuals with sporadic AD due to mutations in the genes encoding for amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2) and usually in the absence of vascular and metabolic risk factors.[22] A recent study on DIAN participants showed a relationship between PA and lower brain amyloid burden in individuals

with ADAD.[25] However, there is a lack of evidence on the association between PA and cognitive performance and AD biomarkers in cerebrospinal fluid (CSF) in ADAD.

In the present study, we aimed 1) to compare cross-sectional PA between MCs and non-carriers (NCs) as a function of estimated years to symptom onset (EYO), 2) to determine the cross-sectional association between PA and cognitive as well as functional parameters, 3) to determine the association between cross-sectional PA and AD biomarkers in the brain and CSF, 4) to determine if current recommendations from World Health Organization and the American College of Sports Medicine[26,27] of at least 150 minutes of PA per week (min/week) may have beneficial effects on global cognition, cognitive decline, and functional status in ADAD.

Methods

Participants

Information regarding participant enrolment and procedures of the DIAN study has previously been described in detail.[24] Briefly, DIAN Study is a longitudinal observational study recruiting participants at risk for known mutations in one the above mentioned three genes. Participants undergo clinical, neuropsychological, imaging, blood and cerebrospinal fluid (CSF) biomarkers analyses.[24,28]

From data release DIAN DF-11 (June 7, 2017), a total of 459 (NC = 184, MC = 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 (IRB) 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.

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.[29] 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.[30] A CDR-SOB score of 3·0-4·0 indicates very mild dementia.[30] Participants also completed the Mini Mental State Examination (MMSE) at baseline.[31]

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.[22,32] 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 from 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 MCs and NCs, 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.[22,32]

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[33]). 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.[26,27] MCs reporting less than 150 minutes of PA per week were categorized into a low PA group (n = 68) and those MCs participating in more than or equal to 150 minutes of activity per week were categorized into a high PA group (n = 156).

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

CSF concentrations of Aβ1-42, total tau (t-tau), and tau phosphorylated at threonine 181 (p-tau181) were measured by Luminex-based immunoassay (AlzBio3, Fujirebio, Ghent, Belgium). Images obtained through positron-emission tomography (PET) with the use of Pittsburgh compound B (PIB) (PIB-PET) were co-registered with individual MRI images for region-of-interest determination. For each region of interest (FreeSurfer defined, MA, USA), 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 PIB SUVR indicates increased binding to fibrillar amyloid. [22,34]

Statistical analysis

All statistical analyses were conducted using JMP®, Version 13·1·0, SAS Institute Inc., Cary, NC, 1989-2016. Differences in clinical characteristics, cognitive, biochemical and imaging parameters between NCs and MCs as well as between MCs with high vs. 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 0·05 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 analysis were adjusted for potential confounders including age, gender, depression (i.e. GDS score), and education.

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

Differences in baseline global cognition (MMSE score) or functional status (CDR-SOB) between MCs and NCs as a function of PA (min/week) were calculated by running covariate-adjusted linear regression models with MMSE or CDR-SOB as dependent variables, PA (min/week) and group (i.e. NCs and MCs) 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 MCs 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, 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 $A\beta_{1-42}$, t-tau, p-tau_{181}, the ratios of t-tau/$A\beta_{1-42}$, p-tau/ $A\beta_{1-42}$, as well as brain amyloid burden) between MCs 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.

Role of the funding source

Data collection and sharing for this project was supported by The Dominantly Inherited Alzheimer's Network (DIAN, U19AG032438) funded by the National Institute on Aging (NIA), the German Center for Neurodegenerative Diseases (DZNE), Raul Carrea Institute for Neurological Research (FLENI), Partial support by the Research and Development Grants for Dementia from Japan Agency for Medical Research and Development, AMED, and the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI).This manuscript has been reviewed by DIAN Study investigators for scientific content and consistency of data interpretation with previous DIAN Study publications. We acknowledge the altruism of the participants and their families and contributions of the DIAN research and support staff at each of the participating sites for their contributions to this study.

Results

Demographics and clinical parameters in MCs and NCs of the DIAN study

Baseline demographics, clinical characteristics, cognitive, biochemical and imaging parameters in MCs and NCs are displayed in Table 1. At baseline, no differences in age, EYO, gender, years of education, and duration of physical activity per week were observed between MCs and NCs.

Association between physical activity (PA) and estimated years from symptom onset (EYO) in mutation carriers (MCs) and non-carriers (NCs)

Interestingly, the level of PA was comparable between MCs (314·2 min/week) and NCs (297·2 min/week) showing no significant difference (p = 0·441) (Table 1). However, when considering the level of PA in MCs and NCs along EYO, we found a significant group*EYO interaction ($F_{[1,368]}$ = 9·018; p = 0·0029). This effect was mostly driven by a significant decrease of PA duration in MCs over time (EYO) (β = -4·915; 95% CI -7·875 to -1·955, p = 0·0012), whereas NCs showed no significant association between PA duration and EYO (β = 1·316; 95% CI -1·460 to 4·093, p = 0·351).

Association between global cognition (MMSE score) / functional status (CDR-SOB score) and physical activity (PA) in mutation carriers (MCs) and non-carriers (NCs)

There was a relatively high trend for a group*PA interaction ($F_{[1,364]}$ = 5·070; p = 0·0593) indicating that MMSE performance was dependent on mutation status and PA. In MCs, an increase in PA was accompanied by higher MMSE-scores (i.e. better global cognition; β = 0·0039; 95% CI 0·0013 to 0·0067, p = 0·004). However, this association was slightly better explained by a quadratic term (β = 0·0044; 95% CI 0·0018 to 0·0071, p = 0·0011) indicating a dose-response relationship of PA on MMSE in MCs (Figure 1A). In contrast, in NCs global cognition seems not to be influenced by PA as there was neither a significant linear

association (p = 0·862) nor a quadratic relationship (p = 0·657) between PA duration and MMSE performance (Figure 1A).

CDR-SOB performance was significantly influenced by mutation status and PA ($F_{[1,364]}$ = 5·578; p = 0·0249). In MCs, lower CDR-SOB (i.e. minor impairment) was significantly associated with an increase in PA (β = -0·002; 95% CI -0·004 to -0·0009, p = 0·0015). Similarly, we found a dose-response relationship of PA on CDR-SOB (Figure 1B) as this association was slightly better explained by a quadratic term (β = -0·002; 95% CI -0·004 to -0·001, p = 0·0007). In NCs there was neither a linear association (p = 0·665) nor a quadratic relationship (p = 0·839) between PA and CDR-SOB performance observable.

Demographics, clinical parameters and AD biomarkers in mutation carriers (MCs) with high (i.e. ≥150 min/week) or low (i.e. <150min/week) physical activity (PA)

Baseline demographics, clinical characteristics, cognitive, biochemical and imaging parameters in MCs with high vs. low PA are displayed in Table 2. Interestingly, MCs with high PA performed better on MMSE (Figure 2A; 28·2 ± 2·5 points vs. 25·1 ± 6·4 points; p < 0·0001) and CDR-SOB (Figure 2B; 0·7 ± 1·4 points vs. 2·0 ± 3·2 points; p < 0·0001) compared to MCs with low PA. In addition, MCs with high PA exhibited lower baseline levels of CSF t-tau (103·7 ± 67·1 pg/mL vs. 1443·3 ± 106·9 pg/mL; p = 0·0019), and p-tau_{181} (60·8 ± 35·6 pg/mL vs. 72·2 ± 42·0 pg/mL; p = 0·0296), lower ratios of CSF t-tau/$Aβ_{1-42}$ (0·25 ± 0·2 vs. 0·43 ± 0·4; p = 0·0002) and p-tau/$Aβ_{1-42}$ (0·15 ±0·2 vs. 0·21 ± 0·1; p < 0·0146), higher levels of CSF $Aβ_{1-42}$ (581·5 ± 305·2 pg/mL vs. 470·6 ± 259·2 pg/mL; p = 0·0178) compared to MCs with low PA (Figure 3).

Association between global cognition (MMSE-score) / functional status (CDR-SOB score) and estimated years from expected symptom onset (EYO) in mutation carriers (MCs) with high (i.e. ≥150 min/week) vs. low (i.e. <150min/week) physical activity (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 = 0·0032; Figure 2c). MCs in the low PA group

revealed greater decline on MMSE-scores with respect to EYO (β = -0·251; 95% CI -0·409 to -0·0924, p = 0·0024) compared to MCs with high PA (β = -0·102; 95% CI -0·139 to -0·065, p < 0·0001). Estimated MMSE score development in MCs with respect to EYO (in 4-year increments and at EYO=0) is displayed in Table 3a illustrating MMSE score benefit (i.e. higher MMSE-score) in MCs with high PA as compared to MCs with low PA. MCs 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) compared to MCs with low PA (MMSE: 23·5±3·2 points; Figure 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 = 0·0233; Figure 2d). MCs in the low PA group revealed greater increase on CDR-SOB with respect to EYO (β = 0·158; 95% CI 0·082 to 0·234, p = 0·001) compared to MCs with high PA (β = 0·089; 95% CI 0·069 to 0·111, p < 0·0001). Estimated CDR-SOB development in MCs with respect to EYO (in 4-year increments and at EYO=0) is displayed in Table 3b illustrating CDR-SOB benefit (i.e. lower CDR-SOB score) in MCs with high PA compared MCs with low PA. MCs 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) than MCs with low PA (i.e. at EYO = 1·1; Figure 5b).

Association between AD biomarkers and estimated years from expected symptom onset (EYO) in mutation carriers (MCs) with high (i.e. ≥150 min/week) or low (i.e. <150min/week) physical activity (PA)

Significant differences in CSF levels of t-tau in relation to PA status (i.e. MCs with high or low PA) and EYO have been detected (PA status*EYO: $F_{[1,185]}$ = 3·963; p = 0·0480; Figure 4). An increase in CSF levels of t-tau was more pronounced in MCs with low activity status with respect to EYO (β = 4·404; 95% CI 1·594 to 7·216, p = 0·0009) compared to MCs with high PA (β = 3·437; 95% CI 2·341 to 4·532, p < 0·0001).

Additionally, ratios of t-tau/$A\beta_{1-42}$ increased in MCs with low PA status with respect to EYO (β = 0·024; 95% CI 0·014 to 0·033, p < 0·0001) compared to MCs with high PA (β = 0·0138;

95% CI 0·009 to 0·0176, p < 0·0001) as indicated by a significant PA status*EYO interaction ($F_{[1,185]}$ = 5·164; p = 0·0244; Figure 4).

For CSF levels of p-tau$_{181}$ ($F_{[1,185]}$ = 1·612; p = 0·206), Aβ_{1-42} ($F_{[1,185]}$ = 0·021; p = 0·973), p-tau/Aβ_{1-42} ratio ($F_{[1,185]}$ = 1·652; p = 0·203), and global Aβ brain burden ($F_{[1,185]}$ = 0·261; p = 0·611) there were no significant interaction effects (Figure 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 MCs reporting less than 150 minutes of PA per week had poorer global cognition and greater decline in global cognition with respect to EYO as compared with 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.[11,15,20,35-39]

By modelling 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), MCs 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 MCs with low PA (i.e. exercise duration < 150 min/week).

In our study the relationship between PA and cognitive performance as well as functional status followed a dose-response curve. A PA duration of ≥ 150 minutes per week 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[26,27] 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 MCs were comparable to those in NCs at baseline and decreased along EYO, 70% of our examined MC population achieved the recommended amount of at least 150 min PA per week. Recently published results demonstrate that participants who reported 150 min or more of vigorous PA per week had no major difficulty in any instrumental or basic activity of daily living and did not show cognitive decline after an 11-year follow-up interval.[40] Additionally, according to WHO recommendations higher PA levels are associated with lower risk of mortality and health problems (e.g. mental health and cardiovascular disease).[41]

In a next step, we examined the relationship between PA and biomarkers of AD. We found that MCs in the high exercise group exhibited lower baseline levels of CSF t-tau and p-tau$_{181}$, higher levels of CSF Aβ_{1-42}, lower ratios of CSF t-tau/Aβ_{1-42} and lower global Aβ brain burden compared to MCs with low PA status. Thus, even after controlling for age, MCs with high PA levels exhibited lower AD-like pathology in CSF and in the brain compared to MCs with low PA levels. In addition, MCs with high PA showed a shift of the cross-sectionally estimated trajectories of CSF levels of t-tau and t-tau/Aβ_{1-42} ratio to the left, i.e. 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 Aβ_{1-42} in LOAD patients.[16,18,19] Furthermore, studies with animal models of AD revealed positive effects of exercise on underlying mechanisms of Aβ and/or tau aggregation in AD transgenic mice.[42-48] However, our results are in contrast with recently published findings in pre-symptomatic MCs of ADAD where the authors found no differences in brain amyloid load, CSF Aβ_{1-42}, or CSF tau levels between low and high exercise MCs.[25] This discrepancy may be due to a different MC population (preclinical and clinical MCs in our study vs. only preclinical MCs in the study by Brown et

al.[25]) and sample size (224 MCs in our study vs. 139 MCs in the study by Brown et al.[25]) between both studies.

The current cross-sectional data cannot clarify the causal direction between PA level and cognition in the examined DIAN cohort. We hypothesized that higher PA levels may result in better cognition which is supported by a large number of cross-sectional and longitudinal studies demonstrating beneficial effects of PA on cognitive function, cognitive decline, AD development, and neuropathological changes associated with AD 1-20. However, we cannot rule out the possibility that in addition worse cognition may lead to lower PA levels.

Several mechanisms have been suggested for explaining the beneficial effects of PA on cognitive function, cognitive decline and neurodegeneration markers: PA positively influences blood pressure, lipids, obesity and inflammatory markers and thus favors vascular health. Other mechanisms of PA on brain health may involve effects on brain plasticity and cognitive reserve, angiogenesis, neurogenesis, and synaptogenesis.[49-51] PA seems to increase molecular growth factors, including brain-derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF-1), both of which play a crucial role in neuroprotection, as well as enhancing neurotransmitter functions.[15,52] Another study found that individuals who carry the apolipoprotein E (*APOE*) ε4 allele, and are therefore at high genetic risk for AD, benefited from an 18-month PA intervention. During the 18-month follow-up, higher levels of reported PA inhibited atrophy of the hippocampus, preserving hippocampal volume and protecting against impairments in episodic memory.[53] Preclinical studies with animal models of AD have demonstrated that both soluble and insoluble Aβ levels were lowered by exercise in AD transgenic mice.[42-48] Thus, the positive influence of PA on cognition might be due to an effect of exercise on underlying mechanisms of Aβ and/or tau aggregation in our ADAD cohort. Studies with LOAD patients revealed that higher levels of self-reported PA have been associated with lower levels of brain amyloid and were associated with greater levels of CSF Aβ (i.e. lower brain amyloid) and lower levels of CSF tau (a marker of neuronal injury).[16,18,19]

Physically active late to middle-aged adults experienced less age-related alterations in Aβ deposition, glucose metabolism, and hippocampal volume compared to physically less active individuals.[17] Moreover, cognitively intact participants (aged 60-95 years) from the Australian Imaging, Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing have been investigated for the association between plasma Aβ and amyloid brain deposition with PA levels, and whether these associations differed between *APOE* ε4 allele carriers and non-carriers. In this study, lower levels of amyloid brain deposition were observed in higher exercising *APOE* ε4 carriers. Thus, PA may be involved in the modulation of pathogenic changes associated with AD.[16]

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 provides 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 compared to the high PA group. Third, we focused our analyses on the MMSE and CDR-SOB scores. Future studies may utilize 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 physical activity and has not being 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, functional status and AD pathology even in individuals with genetically-driven ADAD. Both directions of causality are plausible (exercise strongly protects against clinical

impairment and/or advancing dementia diminishes exercise). 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 counselled to pursue a physically active lifestyle.

Research in context

Evidence before this study

We searched PubMed for articles published up to November, 2017, 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 pathological changes associated with Alzheimer`s disease (AD) as well as on cognitive function, cognitive decline and AD risk in elderly people. None of the reviewed studies directly examined the impact of PA on cognition and functional performance in patients with autosomal dominant Alzheimer's disease (ADAD). Only one study investigated the relationship between PA and cerebral amyloid load in ADAD. Thus, the putative effects of PA on cognitive performance and cerebrospinal fluid (CSF) biomarkers in individuals with ADAD require further investigation.

Added value of this study

Our results are the first, supporting a beneficial effect of PA on cognition and dementia signs and symptoms in individuals with genetically driven ADAD.

For the first time, we report the influence of PA on cognition and functional status in MCs as a function of their estimated years from expected symptom onset. Additionally, we showed that higher PA is associated with less AD-like pathology in CSF. Finally, we found that high PA leads to better cognitive outcome at expected symptom onset and delays the diagnosis of very mild dementia.

Implications of all the available evidence

A physically active lifestyle seems to play an important role in slowing the development and progression of ADAD. We could demonstrate a putative effect of PA on cognitive performance, functional status, and AD biomarkers in individuals with ADAD.

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SM, JCM and CL participated in study concept and design. CL, OP, HRS, SG, MJ, JMR, RNM, ED, PRS, BG, MR, NGR, JL, AD, JV, SS, CX, TB, VB, CLM, RS, RJB and JCM participated in the acquisition, analysis, or interpretation of data, and in the critical revision of the manuscript. SM and CL drafted the manuscript. SM did the statistical analysis.

Declaration of interests

SM, OP, SG, MJ, BG, ED, MR, NGR, AD, JV, VB, CX, TB, CLM, RS, and CL report no disclosures or potential conflicts of interest. JL received personal fees from Aesku, Bayer Vital, Willi Gross Foundation, Axon Neuroscience, Ionis Pharmaceuticals and non-financial support from Abbvie, all outside the submitted work. RJB has received personal compensation for activities with Link Medicine, JAI, Bristol-Myers Squibb Company, Pfizer Inc., Merck, SPRI, Elan Corporation, Eisai Inc., and Medtronic, Inc., received royalty payments from Washington University, and received research support from Astra Zeneca

Pharmaceuticals and Merck & Co., Inc. RNM is the founder and owns stock in Alzhyme and KaRa Minds Institute. HRS has received personal compensation for activities with Pfizer and Wyeth and is the Western Australian Site Neuropsych Lead for TOMMORROW Study by the Takeda Pharmaceuticals. JCM reports disclosures: Neither Dr. Morris nor his family owns stock or has equity interest (outside of mutual funds or other externally directed accounts) in any pharmaceutical or biotechnology company. Dr. Morris has participated or is currently participating in clinical trials of anti-dementia drugs sponsored by the following companies: Janssen Immunotherapy, and Pfizer. Dr. Morris has served as a consultant for Lilly USA. He receives research support from Eli Lilly/Avid Radiopharmaceuticals and is funded by NIH grants # P50AG005681; P01AG003991; P01AG026276 and U19AG032438". JMR reports research support from NIH, Biogen Idec, and Eli-Lilly during the conduct of this study which is outside of the submitted work. PRS has received speaking fees from Janssen Pharmaceuticals and philanthropic support for the DIAN study from the Wicking and Mason Trusts. SS received research support from Functional Neuromodulation, Biogen, Merck, Genentech, Roche, Lilly, and Avid Radiopharmaceuticals. He received consultation fees from Biogen, Merck, Piramal, Lilly, Genentech, and Roche. He owns no stock options or royalties and he reports no conflict of interest with this work.

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Table 1. Baseline demographics, clinical characteristics, cognitive, biochemical and imaging parameters in mutation carriers (MCs) and non-carriers (NCs).

Baseline Characteristic	**Mutation-Carriers* (n=224)**	**Non-Carriers (n=148)**	**p-value**
Age (years)	38·4 (9·9)	38·8 (10·4)	0·696
Est. Years till Symptom Onset	-8·3 (9·4)	-8·2 (11·5)	0·913
Gender (Females, %)	124 (55)	88 (59)	0·434
Education (years)	13·0 (3·2)	14·5 (2·9)	0·103
GDS	2·5 (2·8)	1·6 (1·9)	**0·0005**
MMSE	27·2 (4·5)	29·0 (1·3)	**<0·0001**
CDR global score	0·2 (0·3)	0·00 (0·0)	**<0·0001**
CDR-SOB	1·9 (3·2)	0·01 (0·3)	**<0·0001**
Physical activity (min/week)	314·2 (216·7)	297·2 (194·5)	0·441
Global PIB-uptake	1·43 (0·4)	1·06 (0·1)	**<0·0001**
CSF $A\beta_{1-42}$ (pg/mL)	547·9 (295·8)	789·7 (287·8)	**<0·0001**
CSF t-tau (pg/mL)	116·0 (83·1)	58·4 (26·5)	**<0·0001**
CSF p-tau_{181} (pg/mL)	64·3 (37·9)	29·5 (10·5)	**<0·0001**
t-tau/ $A\beta_{1-42}$ ratio	0·31 (0·3)	0·08 (0·03)	**<0·0001**
p-tau/ $A\beta_{1-42}$ ratio	0·16 (0·1)	0·04 (0·02)	**<0·0001**

Data are mean (SD) or number (%). GDS=Geriatric Depression Scale, MMSE=Mini Mental State Examination, CDR=Clinical Dementia Rating scale, SOB=Sum of Boxes, Global PIB-uptake=global cerebral Aβ burden as measured by ^{11}C-Pittsburgh Compound-B PET, CSF=cerebrospinal fluid, Aβ=amyloid-β_{1-42}, t-tau=total tau, p-tau= phosphorylated tau. * thereof n=165 PSEN1 mutation-carriers, n=20 PSEN2 mutation-carriers, and n=39 APP mutation-carriers.

Table 2. Baseline demographics, clinical characteristics, cognitive, biochemical and imaging parameters in mutation carriers (MCs) with high (i.e. ≥150 min/week) or low (i.e. <150 min/week) physical activity (PA).

Baseline Characteristic	**high active MCs (n=156)**	**low active MCs (n=68)**	**p-value**
Age (years)	37·3 (10·2)	41·1 (8·9)	**0·0084**
Est. Years till Symptom Onset	-9·6 (8·4)	-5·3 (8·2)	**0·0012**
Gender (Females, %)	84 (54%)	42 (62%)	0·272
Education (years)	14·1 (3·1)	13·8 (3·3)	0·496
GDS	2·1 (2·6)	2·5 (2·6)	0·252
MMSE	28·2 (2·5)	25·1 (6·4)	**<0·0001**
CDR global score	0·2 (0·3)	0·4 (0·4)	**0·0002**
CDR-SOB	0·7 (1·4)	2·0 (3·2)	**<0·0001**
Physical activity (min/week)	425·5 (159·2)	58·9 (52·4)	**<0·0001**
Global PIB-uptake	1·39 (0·3)	1·52 (0·5)	0·0539
CSF $A\beta_{1-42}$ (pg/mL)	581·5 (305·2)	470·6 (259·2)	**0·0178**
CSF t-tau (pg/mL)	103·7 (67·1)	144·3 (106·9)	**0·0019**
CSF p-tau_{181} (pg/mL)	60·8 (35·6)	72·2 (42·0)	**0·0296**
t-tau/ $A\beta_{1-42}$ ratio	0·25 (0·2)	0·43 (0·4)	**0·0002**
p-tau/ $A\beta_{1-42}$ ratio	0·15 (0·1)	0·21 (0·2)	**0·0146**

Data are mean (SD) or number (%). MCs=Mutation Carriers, GDS=Geriatric Depression Scale, MMSE=Mini Mental State Examination, CDR=Clinical Dementia Rating scale, SOB=Sum of Boxes, Global PIB-uptake= global cerebral Aβ burden as measured by ^{11}C-Pittsburgh Compound-B PET, CSF=cerebrospinal fluid, Aβ=amyloid-β_{1-42}, t-tau=total tau, p-tau= phosphorylated tau. MCs with high PA reported 150 or more minutes of exercise per week, MCs with low PA reported less than 150 minutes per week of exercise.

Table 3a. Estimated MMSE score development in MCs with high (i.e. ≥150 min/week) or low (i.e. <150 min/week) physical activity (PA) with respect to years from expected symptom onset (EYO).

EYO	MMSE in high active MCs	MMSE in low active MCs	MMSE score profit in high active MCs compared to low active MCs
-20 to -16	29·3 (5·3)	29·1 (6·2)	+0·2
-15 to -11	28·6 (4·1)	27·5 (4·3)	+1·1
-10 to -6	27·9 (2·3)	25·9 (2·7)	+2·0
-5 to -1	27·3 (2·4)	24·4 (2·9)	+2·9
0	26·9 (2·1)	23·5 (3·2)	+3·4
1 to 5	26·5 (3·0)	22·5 (3·7)	+4·0
6 to 10	25·8 (3·2)	21·0 (4·3)	+4·9
11 to 15	25·2 (4·1)	19·4 (5·5)	+5·7
16 to 20	24·5 (5·8)	17·9 (7·4)	+6·6

Data are displayed as mean (SD). MCs=Mutation Carriers, EYO=Estimated years until symptom onset, MMSE=Mini Mental State Examination. MCs with low PA reported less than 150 minutes per week of exercise, MCs with high PA reported 150 or more minutes of exercise per week.

Table 3b. Estimated CDR-SOB score development in MCs with high (i.e. ≥150 min/week) or low (i.e. <150 min/week) PA levels with respect to years from expected symptom onset (EYO).

EYO	CDR-SOB in high active MCs	CDR-SOB in low active MCs	CDR-SOB difference in high active MCs compared to low active MCs*
-20 to -16	0·14 (0·8)	0·02 (1·1)	0·1
-15 to -11	0·59 (0·5)	0·77 (1·2)	-0·2
-10 to -6	1·03 (0·4)	1·56 (0·9)	-0·5
-5 to -1	1·47 (0·4)	2·35 (0·8)	-0·9
0	1·56 (0·8)	2·82 (0·6)	-1·3
1 to 5	2·01 (0·3)	3·30 (0·5)	-1·3
6 to 10	2·45 (1·1)	4·09 (0·8)	-1·6
11 to 15	2·90 (1·2)	4·88 (1·4)	-1·9
16 to 20	3·34 (1·4)	5·67 (1·6)	-2·3

Data are displayed as mean (SD). MCs=Mutation Carriers, EYO=Estimated years until symptom onset, CDR-SOB=Clinical Dementia Rating Scale Sum of Boxes (lower score indicates lower impairment). MCs with low PA reported less than 150 minutes per week of exercise, MCs with high PA reported 150 or more minutes of exercise per week. *negative signs indicate that the high PA group had a lower CDR-SOB score (i.e. better functional status) by the given value at the specified EYO.

Figure 1

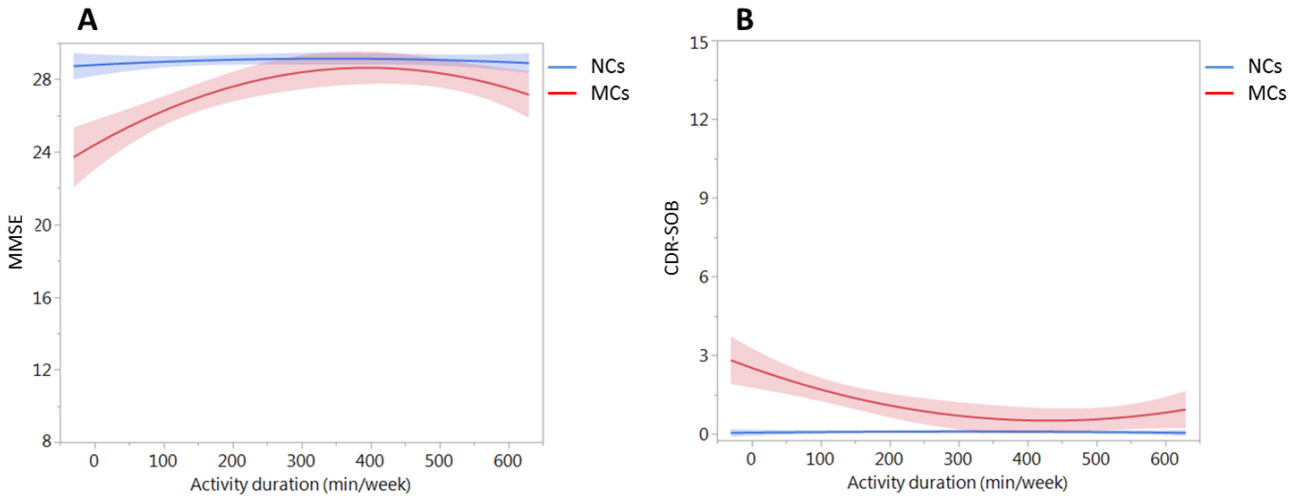

A
MMSE
28
24
20
16
12
8
0
100
200
300
400
500
600
Activity duration (min/week)
NCs
MCs
B
CDR-SOB
15
12
9
6
3
0
0
100
200
300
400
500
600
Activity duration (min/week)
NCs
MCs

Figure 2

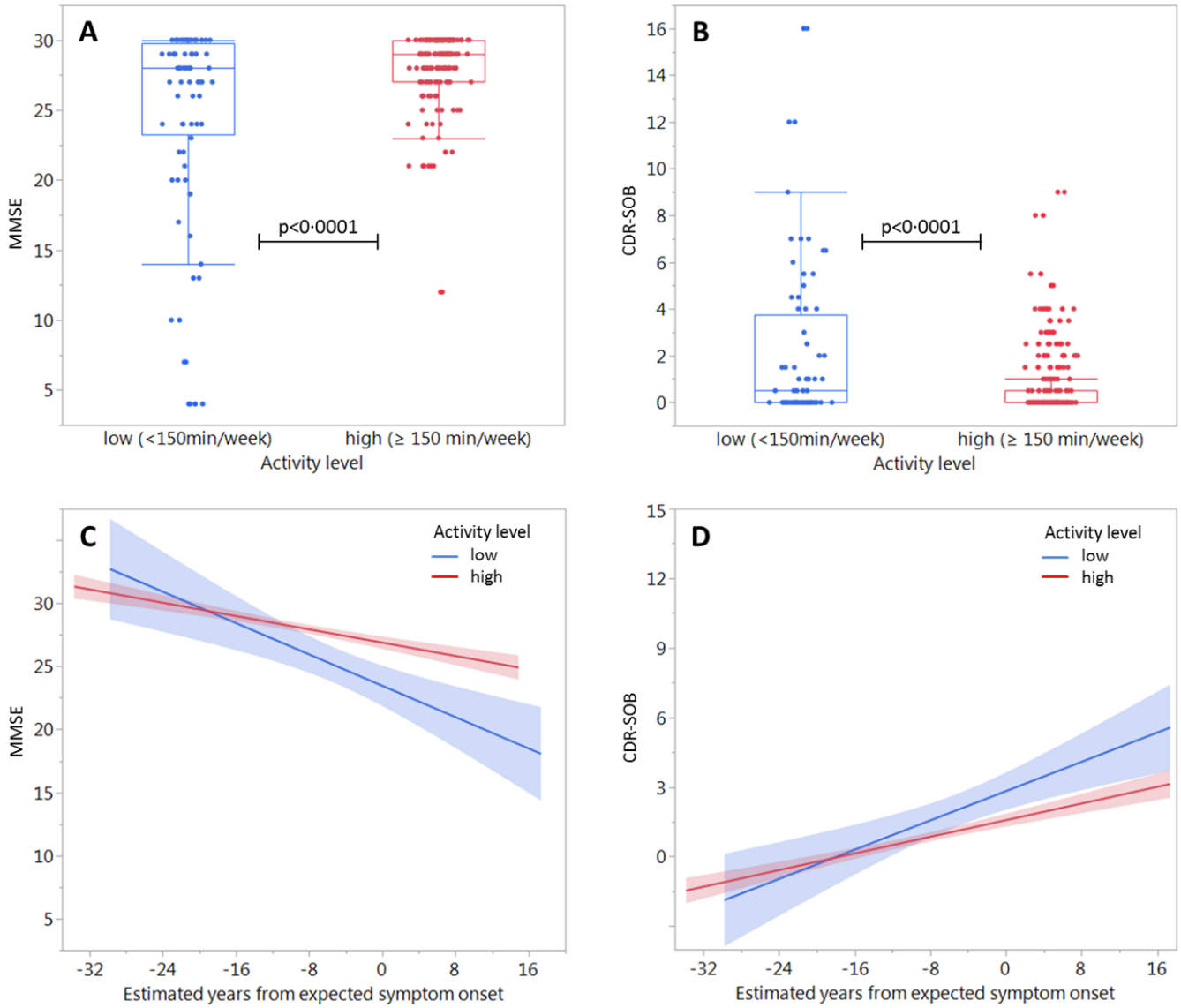

A
MMSE
30
25
20
15
10
5
p<0·0001
low (<150min/week)
high (≥ 150 min/week)
Activity level
B
CDR-SOB
16
14
12
10
8
6
4
2
0
p<0·0001
low (<150min/week)
high (≥ 150 min/week)
Activity level
C
Activity level
low
high
MMSE
30
25
20
15
10
5
-32
-24
-16
-8
0
8
16
Estimated years from expected symptom onset
D
Activity level
low
high
CDR-SOB
15
12
9
6
3
0
-32
-24
-16
-8
0
8
16
Estimated years from expected symptom onset

Figure 3

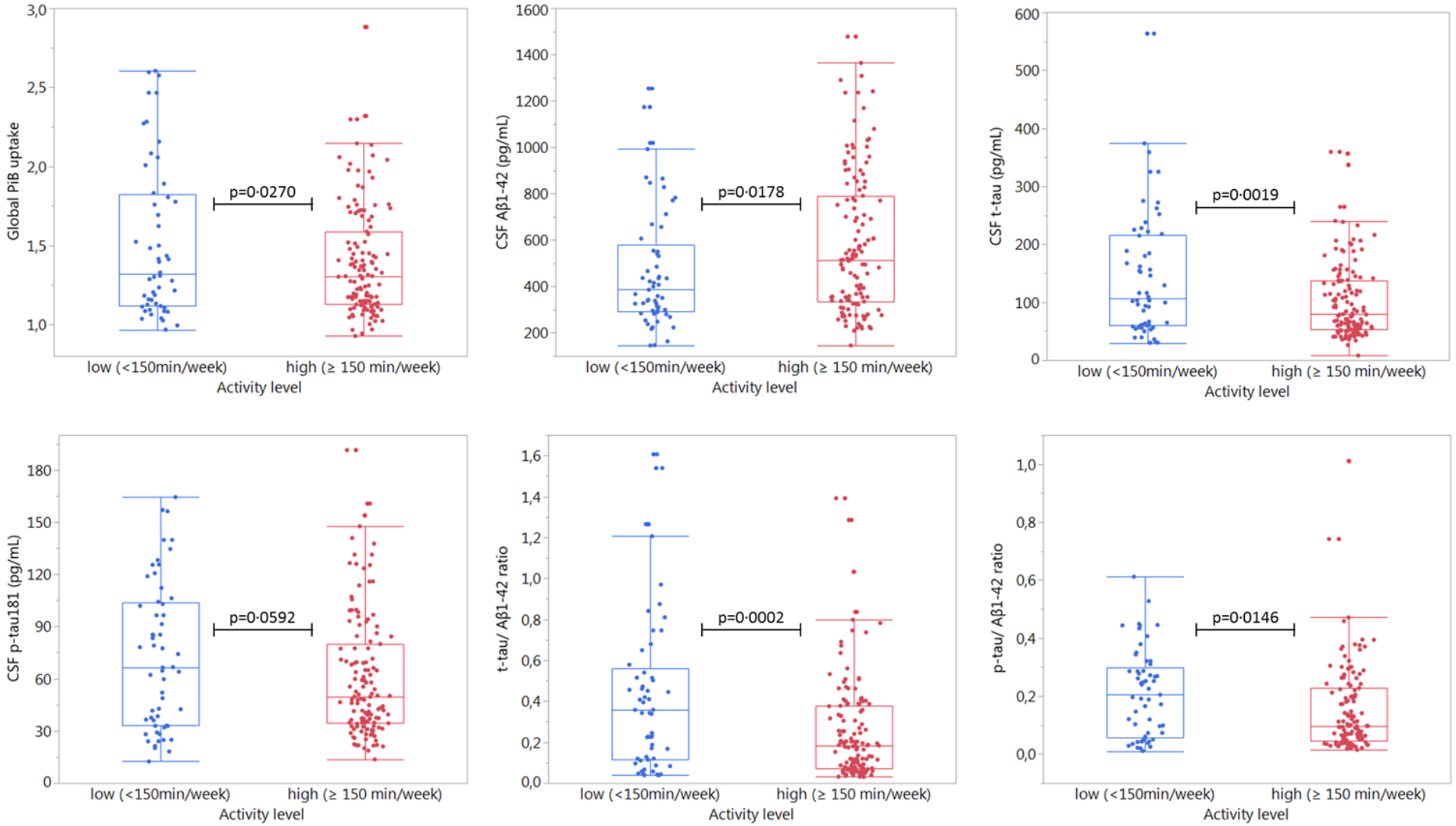

Global PiB uptake
3,0
2,5
2,0
1,5
1,0
p=0·0270
low (<150min/week)
high (≥ 150 min/week)
Activity level
CSF Aβ1-42 (pg/mL)
1600
1400
1200
1000
800
600
400
200
p=0·0178
low (<150min/week)
high (≥ 150 min/week)
Activity level
CSF t-tau (pg/mL)
600
500
400
300
200
100
0
p=0·0019
low (<150min/week)
high (≥ 150 min/week)
Activity level
CSF p-tau181 (pg/mL)
180
150
120
90
60
30
0
p=0·0592
low (<150min/week)
high (≥ 150 min/week)
Activity level
t-tau/ Aβ1-42 ratio
1,6
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
p=0·0002
low (<150min/week)
high (≥ 150 min/week)
Activity level
p-tau/ Aβ1-42 ratio
1,0
0,8
0,6
0,4
0,2
0,0
p=0·0146
low (<150min/week)
high (≥ 150 min/week)
Activity level

Figure 4

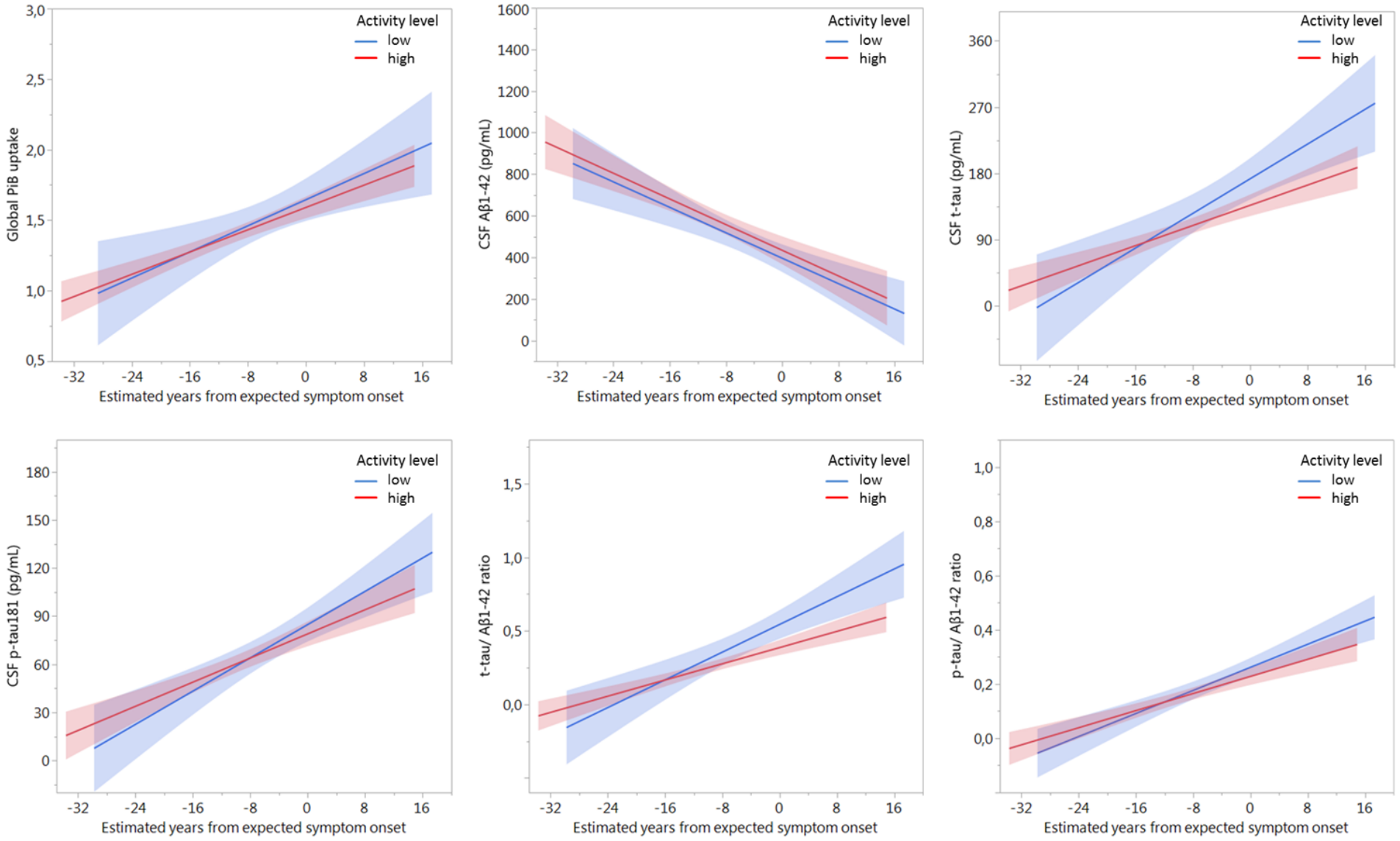
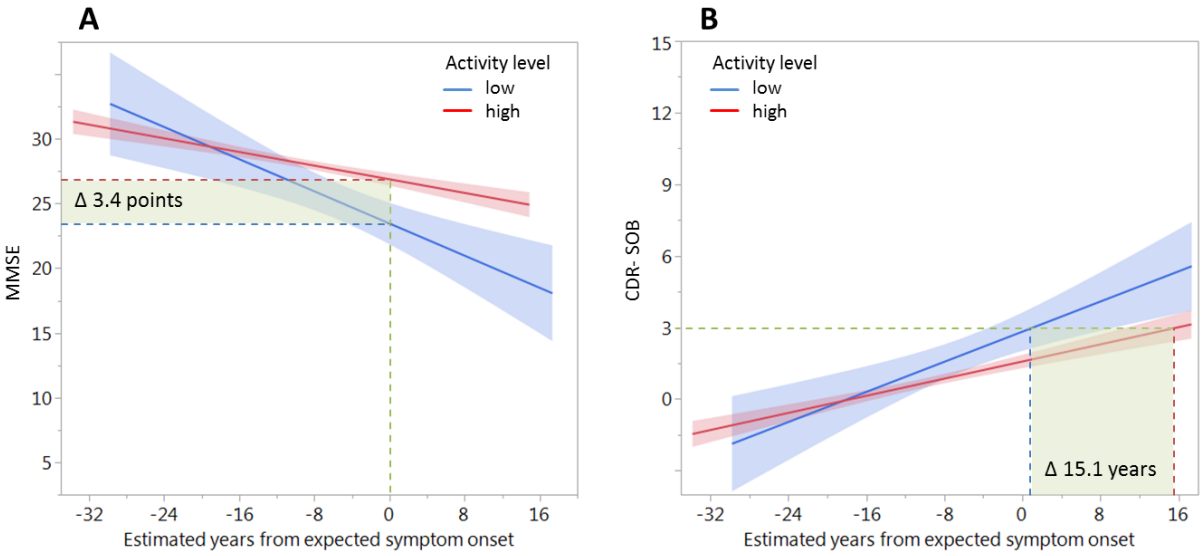

Activity level
low
high
Global PiB uptake
3,0
2,5
2,0
1,5
1,0
0,5
CSF Aβ1-42 (pg/mL)
1600
1400
1200
1000
800
600
400
200
0
CSF t-tau (pg/mL)
360
270
180
90
0
CSF p-tau181 (pg/mL)
180
150
120
90
60
30
0
t-tau/ Aβ1-42 ratio
1,5
1,0
0,5
0,0
p-tau/ Aβ1-42 ratio
1,0
0,8
0,6
0,4
0,2
0,0
-32
-24
-16
-8
0
8
16
Estimated years from expected symptom onset

Figure 5


A
Activity level
low
high
Δ 3.4 points
MMSE
30
25
20
15
10
5
-32
-24
-16
-8
0
8
16
Estimated years from expected symptom onset
B
Activity level
low
high
CDR- SOB
15
12
9
6
3
0
Δ 15.1 years
-32
-24
-16
-8
0
8
16
Estimated years from expected symptom onset

Legends:

Figure 1A: Global cognitive function as assessed by the Mini Mental State Examination (MMSE) score in mutation-carriers (MCs) and non-mutation carriers (NCs) with respect to time spent in leisure-time exercise activities. The quadratic model fit lines are presented in blue for NCs and red for MCs. **B:** Functional and cognitive performance as assessed by the Clinical Dementia Rating scale sum of boxes (CDR-SOB) in MCs and NCs with respect to time spent in leisure-time exercise activities. The quadratic model fit lines are presented in blue for NCs and red for MCs.

Figure 2A: Baseline levels of global cognitive function as assessed by the Mini-Mental-State Examination (MMSE) score in mutation-carriers (MCs) with either high (i.e. ≥ 150 min/week) or low (i.e. <150 min/week) physical activity (PA). **B:** Baseline levels of Clinical Dementia Rating scale sum of boxes (CDR-SOB) in MCs with either high or low PA. **2C:** MMSE as a function of estimated years from expected symptom onset (EYO) in MCs with either high or low PA status. The regression lines are presented in red for the high PA group and blue for the low PA group. **2D:** CDR-SOB as a function of EYO in MCs with either high or low PA. The regression lines are presented in red for the high PA group and blue for the low PA group.

Figure 3: Baseline levels of AD biomarkers (i.e. global PiB uptake, CSF levels of $A\beta_{1-42}$, t-tau, p-tau_{181}, as well as t-tau/$A\beta_{1-42}$, and p-tau_{181}/$A\beta_{1-42}$ ratio) in mutation-carriers (MCs) with either high (i.e. ≥ 150 min/week) or low (i.e. <150 min/week) physical activity (PA) status.

Figure 4: AD biomarkers (i.e. global PiB uptake, CSF levels of $A\beta_{1-42}$, t-tau, p-tau_{181}, as well as t-tau/$A\beta_{1-42}$, and p-tau_{181}/$A\beta_{1-42}$ ratio) as a function of estimated years from expected symptom onset (EYO) in mutation-carriers (MCs) with either high (i.e. ≥ 150 min/week) or

low (i.e. <150 min/week) physical activity (PA) status. The regression lines are presented in red for the high PA group and blue for the low PA group.

Figure 5A: Estimated difference in global cognitive function as assessed by the Mini Mental State Examination score (MMSE) between mutation-carriers (MCs) with either high (i.e. ≥ 150 min/week) or low (i.e. <150 min/week) physical activity (PA) at expected symptom onset (i.e. EYO=0). MCs with high PA score 3.4 points better on MMSE evaluation compared to MCs with low PA at expected symptom onset. The dotted line in red reflects MMSE score of the high PA group (26·9±2·1 points) and in blue for the low PA group (23·5±3·2 points) at EYO=0. **5B:** Estimated difference in years matching the diagnosis of very mild dementia according to Clinical Dementia Rating scale sum of boxes (CDR-SOB) between MCs with either high or low PA. MCs with high PA reveal a CDR-SOB score of 3·0 (i.e. very mild dementia) 15·1 years later than MCs with low PA. The dotted line in red reflects EYO of the high PA group (EYO=16·2) and in blue for the low PA group (EYO=1·1) when both groups match the criteria of very mild dementia according to CDR-SOB.