

**Investigating fitness and physical activity increase as secondary prevention of
Alzheimer's disease in a sports interventional approach**

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Modulating effects of fitness and physical activity on Alzheimer's disease: Implications from a six-month randomized controlled sports intervention

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Abstract

Background: Physical activity and fitness are major targets in Alzheimer's disease (AD) preventive research. However, current research is heterogeneous and often disregards the relationship between these parameters and disease outcomes.

Objective: To assess the effects of physical activity and fitness on AD within the context of a multicomponent sports intervention.

Methods: 46 participants with early-stage AD (mean age 70 ± 7 years, 18 women, mean Montreal Cognitive Assessment (MoCA) score 19 ± 5) were included in a six-month randomized controlled trial (Dementia-MOVE), participating in either a multicomponent sports intervention or a control condition with a psychoeducational program. The modulating effect of fitness and physical activity changes on AD outcome parameters such as cognition, function and cerebral brain structure from 3T-MRI were examined using multiple linear regression analyses.

Results: An increase in $VO_2\text{max}$ was associated with assignment to the intervention group ($p = 0.016$), lower baseline fitness ($p = 0.001$), and an increased rate of physical activity ($p = 0.046$). Only in the intervention group, $\Delta VO_2\text{max}$ had a beneficial modulating effect on the MoCA score ($p = 0.039$), the executive functions ($p = 0.017$) and regional brain volumes of the temporal lobe, e.g., the hippocampus ($p = 0.044$). High daily step count was associated with preserved executive functions ($p = 0.001$), and caregivers' quality of life ($p \leq 0.001$) in the overall sample.

Conclusions: Our results confirm that multicomponent exercise improves cardiorespiratory fitness in AD, which is associated with advantageous developments in cognitive performance and preservation of brain structure. These findings suggest that especially patients with comparably worse cognition and fitness benefit and should be encouraged for activity engagement.

Keywords

Alzheimer's disease, exercise, fitness development, intervention, lifestyle modification, magnetic resonance imaging, mild cognitive impairment, neurodegeneration, neuroimaging

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Introduction

Aging society and rising life expectancy are associated with an increased prevalence of chronic diseases like dementia, accompanied by higher rates of care dependency and mortality, as well as elevated treatment costs.¹ Looking at Alzheimer's disease (AD) as the most common type of dementia, the disease often progresses over years, from mild cognitive impairment (MCI) or early manifest AD, characterized by clinically assessed minor cognitive limitations, to increasing symptom burden and disability as the neurodegeneration advances.^{2,3} Aside from pharmacological therapies, exercise that increases cardiorespiratory fitness (CRF) has previously been shown to be an effective, low-cost, and easily accessible treatment option for both elder individuals at risk, as well as patients diagnosed with amnesic MCI (aMCI) or AD.^{4,5}

While there is increasing evidence that general physical activity, defined in contrast to sedentary behavior, can protect against cognitive decline,^{6,7} the underlying effects at the cerebral level with regard to neurodegeneration are still subject to intensive research. Current findings suggest that physical activity influences neuronal molecular pathways, optimizes brain metabolism, and increases regional cerebral blood flow.^{8,9} Neuroimaging studies based on these considerations show that high physical activity levels and short-term interventions for up to six months could influence brain structure in AD-affected regions such as the hippocampus and further regions of the temporal lobe. Yet their findings are inconsistent due to the general heterogeneity of study designs and often not clearly characterized study populations.^{10–13} Thus, the question of how exactly fitness and physical activity affect brain integrity during neurodegeneration still remains unanswered.

Furthermore, previous exercise trials often fail to consider the complex mutual relation of physical activity and fitness improvement in the context of a sports intervention; hence, their interacting effect on the different aspects of AD pathology is unclear.¹⁴ Establishing a suitable intervention and finding the optimal exercise dose for the elderly and cognitively impaired population is therefore challenging but at the same time highly clinically relevant. So far, multicomponent exercise interventions comprising moderate-to-vigorous physical activity (MVPA) at least twice a week for a minimum duration of three to six months appear to be the most promising for increasing CRF.^{15,16} In line with these findings, the World Health Organization (WHO) has also published recommendations on the rate of physical activity in elder subjects, constituting at least 150–300 min of moderate-intensity or at least 75–150 min of vigorous-intensity aerobic physical activity per week, with the recommendation to perform multicomponent activity to prevent falls and increase muscle strength.¹⁷ Additional psychoeducational and lifestyle-modifying programs, for instance based on the FINGER study design, can also increase

adherence to and acceptance of such recommendations and interventions,^{18,19} pointing again to the relevance of multicomponent lifestyle interventions.

The Dementia-MOVE trial (Multi-Objective Validation of Exercise in Dementia) therefore examined the influence of a six-month multicomponent exercise intervention based on these previous recommendations, while adjusted to the needs of people with AD. Fitness development, the influence of CRF and activity changes on the different domains and facets of AD progression are analyzed for a holistic approach to the disease.

We expect that people with AD participating in the exercise intervention program will improve their fitness compared to a control group attending a psychoeducational program only. We hypothesize that increased fitness and a higher level of physical activity due to participation in the intervention program leads to a positive impact on cognitive performance, neuropsychiatric health and brain integrity in AD. As an underlying goal, we examine the feasibility and acceptance of this intensified program as a treatment option in a cohort of elderly people affected by AD.

Methods

Study design and participants

The study Dementia-MOVE is a randomized controlled clinical trial with two arms, including an intervention group receiving a six-month multicomponent exercise training and a control group undergoing a psychoeducational program.²⁰ In summary, a total of 46 people aged between 50 to 80 years with early AD, who were cognitively and physically eligible for a physical exercise program, were recruited at the memory clinic of the Department of Neurology of the RWTH Aachen University Hospital (UKA), and via advertising and search in newspapers (see Figure 1). All participants were characterized as having mild cognitive impairment (MCI) or mild AD with a cerebrospinal fluid (CSF) constellation of amyloid- β 1-42 or amyloid- β 42/40 ratio (A), phospho-tau (T), and tau (N) based on Jack et al. (2018), resulting in their characteristic ATN-status alongside the AD-continuum.²¹ According to this, all participants included showed a pathological amyloid CSF concentration (A+), with phospho-Tau CSF concentrations in either elevated (A⁺T⁺; $n=32$) or normal range (A⁺T⁻, $n=9$). In cases where CSF biomarkers were not available ($n=5$), the diagnosis of AD was based on neuroimaging and clinical evaluation (i.e., neurological examination, and neuropsychological assessment) as part of an expert consensus at the memory clinic at UKA. All participants presented an early-stage disease with a Clinical Dementia Rating scale (CDR) ≤ 1 . Exclusion criteria mainly included severe systemic, cardiopulmonary, orthopedic and/or psychiatric diseases (for a complete overview of the inclusion

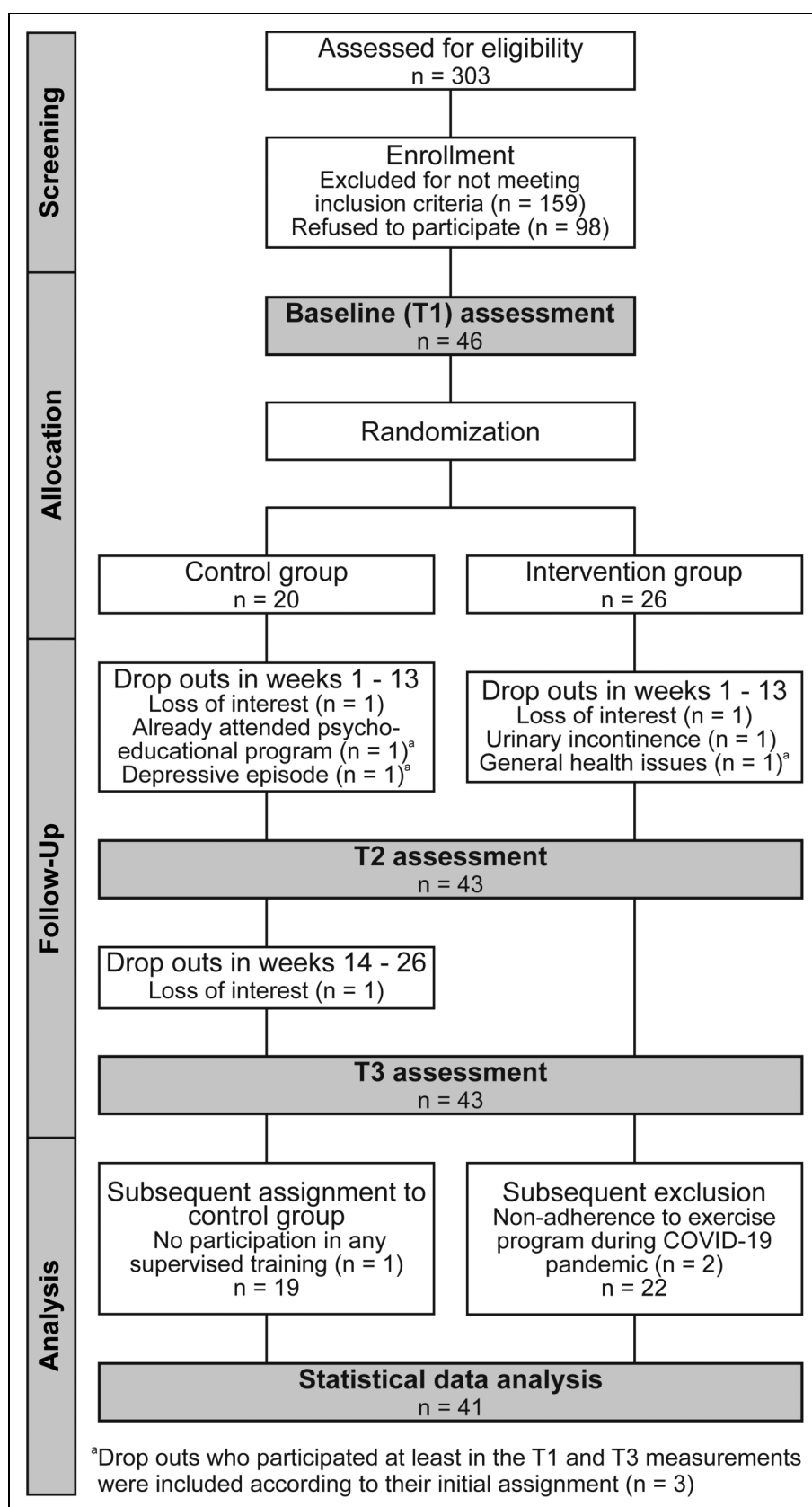


Figure 1. Participant flow chart of the screening and intervention period and the subsequent analysis. A total of 41 patients (22 in the intervention group and 19 in the control group) were finally included for statistical data analysis. Note that even when nine participants dropped out of the program, four participants still agreed to participate in the outcome assessments.

and exclusion criteria, see also Supplemental Table 1). Sample size calculations were based on power analyses which were derived from our primary outcome parameter presented by metabolic MR imaging and our previous results in this context.^{20,22,23} After performing baseline assessments at time point T₁, participants were randomized into either the exercise intervention group ($n = 26$) or the control group ($n = 20$) by a blinded member of the study team using the WINPEPI software.²⁴ Stratification followed age and fitness level, as determined via VO₂max, or in case of non-availability, the result of the 6-min walk test (6MWT). The site of residency was further considered when allocating between Aachen and Simmerath. In case of unequal numbers of participants, allocation was performed in favor of the intervention group.

The study and all protocol changes were approved by the Ethics Committee at the Medical Faculty of the Rheinisch-Westfälische Technische Hochschule Aachen (RWTH Aachen) (EK 306/18) and were performed according to the latest Declaration of Helsinki. All participants gave written informed consent for study participation and protocol changes. The trial was registered at ClinicalTrials.gov (NCT03939286). Further details on the study design of the Dementia-MOVE protocol have been previously published.²⁰

The multicomponent intervention program

A detailed overview of all intervention components is presented in Figure 2. The intervention program started after randomization and took place for a total duration of 26 weeks (six months plus two weeks for optional compensation on missed appointments). Participants assigned to the intervention group attended a supervised exercise session for 60 min per week, taking place at two study sites, the UKA or the hospital Eifelklinik St Brigida in Simmerath, located approximately 20 km south-east of Aachen, with its affiliated professional physiotherapy practice. The program was homogenized between both sites and included aerobic, resistance, and coordination exercises. It was supervised by physiotherapists and members of the study team. Sports groups usually consisted of about five participants per group, therefore assuring an optimized supervision and individualized guidance of the sports program. During the first supervised training session, the optimal exercise load for the program was determined for each individual: (1) ergometer wattage was estimated from 6-MWT distance according to Luxton et al.,²⁵ and (2) load for a moderate resistance training intensity was calculated according to the Epley formula for 40% of one-repetition-maximum.²⁶ Over the course of the intervention period, the exercise load was then gradually increased according to moderate-to-vigorous physical exertion regularly surveyed using the Borg RPE-scale during the training sessions.²⁷ An exemplary training plan including mean initial exercise loads is provided in the Supplemental Table 2.

In addition to the participation in the supervised training program, participants of the intervention group were further instructed to perform a moderate-to-vigorous intensity home-based training for at least 30 min per week, as well as stretching and toning exercises for at least 15 min twice per week, following current recommendations on repetitive physical exercise.²⁸ Supporting training cards from the German Federal Centre for Health Education (BZgA) for the stretching and toning exercises were distributed to the intervention participants.²⁹

Furthermore, both groups participated in monthly psychoeducational lectures at both study sites, respectively, with a focus on lifestyle modifying factors, disease management, and help offers, as well as therapy options based on the content of the FINGER study (see Figure 2),³⁰ thus, also controlling for the social aspect of the intervention as control condition.

During the first COVID-19 lockdown in Germany, the supervised exercise program was substituted by a home-based training for nine weeks from March to May 2020, for 18 participants. Exercises in the home-based training were chosen to optimally resemble the supervised training and to address the same muscle groups without resorting to training machines, yet participants were allowed to implement available home gym equipment at any time. To optimize coordination training at home, the participants received an MFT Fun Disc® balance plate, which was also used during the training sessions at both study sites. Instructions for a homogenized home-based training were sent in written form and orally explained to all participants of the sports groups and their relatives (see also Supplemental Table 2). The psychoeducational topics were summarized in paper form and sent to all participants during the lockdown period. The discussion of these lectures and a check for training adherence was carried out by weekly telephone calls through the study team. Since the T₃ assessment of five participants was not feasible at that time, the intervention was extended for a further nine weeks for these individuals to maintain the intervention effect, until the lockdown was terminated, and assessments could be safely performed.

Measuring fitness and physical activity

Aerobic fitness was assessed via estimation of VO₂max, a well-established and validated parameter in exercise testing, which defines a person's maximum capacity to absorb and metabolize oxygen.³¹ We therefore performed a submaximal ergometer test on a Lode Corival CPET® device following a modified Astrand protocol.³² Additionally, the 6-MWT was performed for an alternative estimation of VO₂max when the participants failed to increase heart frequency during the Astrand protocol, for instance, due to β -blocker intake or orthopedic impairment impeding ergometer cycling, which can be common in an elder population.³³

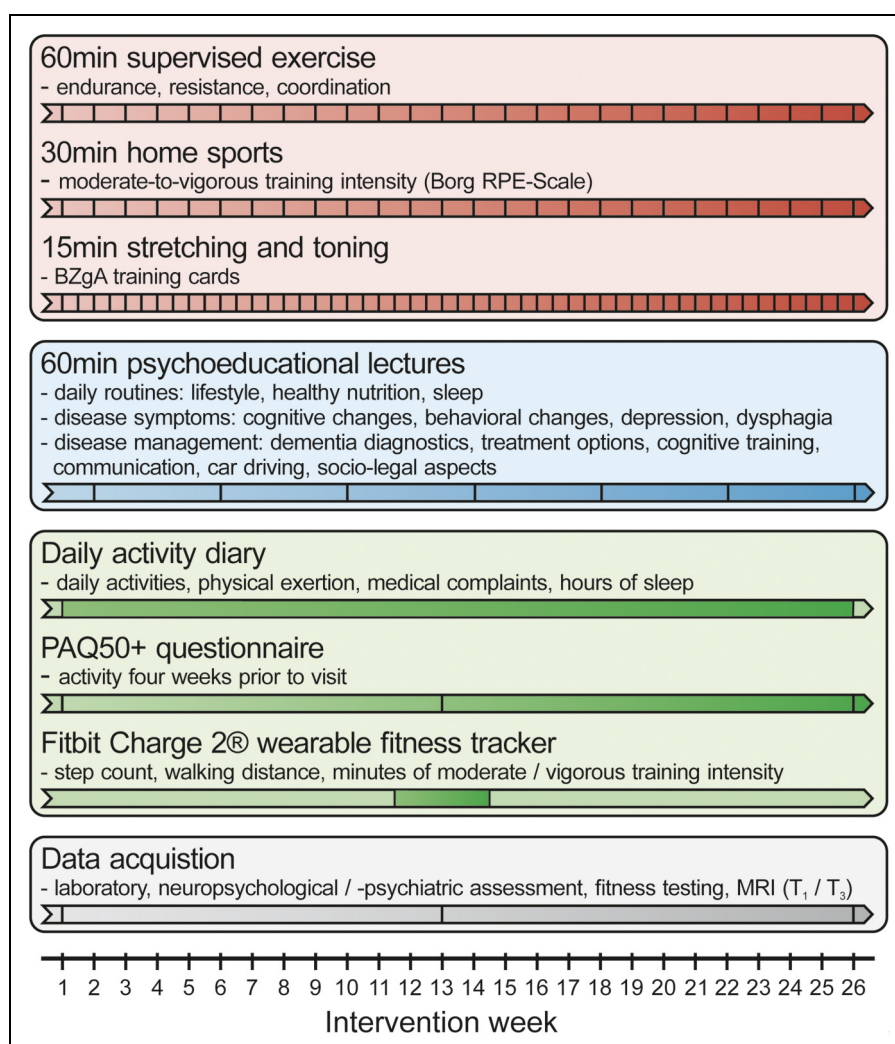


Figure 2. Outline and timeline of the multicomponent intervention design with its three main components: the supervised exercise, the psychoeducation program and the different methods for activity monitoring as well as the three acquisition time points. Borg RPE-Scale: Borg Rating of Perceived Exertion Scale; BZgA: German Federal Centre for Health Education.

Furthermore, handgrip strength was measured using a Saehan® hand dynamometer,³⁴ as well as postural stability via the MFT-S3-Check® system, which records stability, sensomotricity, and symmetry data of two passes, with a balance plate tilting front/back and left/right, respectively.³⁵ Previous studies have associated weak performance in both parameters with cognitive decline.^{36,37} All fitness assessments were performed at time point T_1 at baseline, after three months at time point T_2 , and after six months at time point T_3 .

A written diary was used to monitor physical activity and compliance throughout the entire duration of the intervention. It was completed by the participants with the help of their caregivers if needed and included space for the participants to record types and duration of daily activities as well as additional information such as subjective exertion during exercise, hours of sleep, medication taken if

necessary, and medical issues occurring during study participation. Filled pages were regularly collected by the study team and checked for missing or incomplete data. In case of such occurrences, the participants and caregivers were re-advised to avoid missing data on previous activities.³⁸

Furthermore, the PAQ50+ questionnaire, which is adapted to physical activity assessment in elder people, was used at each assessment time point four weeks prior to the visits T_1 , T_2 , and T_3 .³⁹ To demonstrate the reliability of these two subjective assessing methods, the Fitbit Charge 2® (Fitbit), a wearable fitness tracker, was distributed to the study participants for an average duration of 14 days around the middle of the intervention period to objectively record activity during that time. The Fitbit registered step count, walking distance, activity minutes of varying intensity, calorie consumption, as well as sleep.

Processing of physical activity and fitness assessment data

A detailed methodological description and comparison of the three assessment methods of physical activity and fitness, i.e., the wearable fitness tracker, the written diary, and the PAQ50+, is presented in our recent publication.³⁸ In short, daily metabolic equivalent of task (MET) scores were calculated based on the different output data as follows:

$$\text{Daily MET} = \sum_{n=1}^A \frac{t_n \times \text{MET}_n}{60}, \quad (1)$$

with A being the number of distinct daily activities performed, t_n the time in minutes spent on activity n , weighted by its individual MET MET_n ; low intensity activities with a MET score <2 were filtered by our algorithm.^{38,40}

A further MVPA score was calculated by summarizing daily moderate and vigorous activity minutes for all three assessing methods. For the diary and the PAQ50+, activity minutes were computed based on the activities' individual MET scores, classifying moderate activity as MET 3–5.9 and vigorous activity as MET >6 according to previous literature.^{41,42}

VO_2max as a measure of CRF was estimated from ergometer testing data according to von Döbeln et al.,⁴³ taking the advanced age and differing body compositions as well as maximum heart rates of an elder study population into account compared to the classic nomogram introduced by Astrand and Rhyming (1954)³²:

$$\text{VO}_2\text{max} = 1.29 \sqrt{\frac{\text{load [kpm]}}{\text{heart rate [at 5–6min, bpm]} - 60}} \times e^{-0.00884 \times \text{age [years]}} \quad (2)$$

For eight participants who were not able to cycle or did not reach a defined threshold heart rate $>110/\text{min}$ during the test protocol on at least one acquisition time point, VO_2max was estimated from the 6-MWT distance according to Burr et al. to avoid inaccuracies in estimation resulting from stronger heart rate deviations of the original Astrand protocol.⁴⁴

For handgrip strength, we focused on the participants' dominant hand (right = 38, left = 2, ambidextrous = 1 of the included subjects). Furthermore, a mean composite score of all postural stability measuring components was calculated, including Z-standardized stability, sensomotoric and symmetry values of the two different passes performed.

Assessment of AD outcome parameters

Neuropsychiatric and cognitive screening. Neuropsychiatric and behavioral symptoms were assessed via questionnaires sent to the participants and their relatives in advance of each assessment appointment T_1 , T_2 , and T_3 . This assessment

included the Quality of Life in AD (QoL-AD),⁴⁵ the German version of the Hospital Anxiety and Depression Scale (HADS-D),⁴⁶ the Neuropsychiatric Inventory Questionnaire (NPI-Q),⁴⁷ as well as the Pittsburgh Sleep Quality Index (PSQ-I).⁴⁸ Absolute questionnaire scores were used for the subsequent analyses. For HADS-D and PSQ-I, higher scores indicate more severe depressive symptoms and worse sleep quality, respectively.

Global cognitive screening was evaluated via the Mini-Mental State Examination (MMSE, at baseline T_1 only),⁴⁹ and the Montreal Cognitive Assessment (MoCA).⁵⁰ Furthermore, a neuropsychological test battery focusing on attention, verbal memory, and executive functions was performed. Alternate versions of the tests were used at the three assessment time points T_1 , T_2 , and T_3 , if available. The attention score comprised cued and non-cued reaction time of the Test of Attentional Performance (TAP),⁵¹ and digit span forward.⁵² Verbal memory was assessed via the California Verbal Learning Test (CVLT).⁵³ Executive functions domain included the Trail Making Test's (TMT) B/A-ratio,⁵⁴ phonemic and semantic word fluency,⁵⁵ digit span backwards,⁵² and the Stroop interference task.⁵⁶ Results of the individual tests were Z-standardized with baseline means and standard deviations as references and then summarized as mean composite scores for each domain.⁵⁷

Structural MRI analysis. All MRI images were acquired on the same 3-Tesla Siemens PRISMA whole-body MR scanner at baseline (T_1) and after the intervention (T_3). Isotropic high-resolution T1-weighted images of the brain were obtained with an MP-RAGE sequence (TR = 2400 ms, TI = 1000 ms, TE = 2.4 ms, FA = 8°, 0.8 mm isotropic resolution). Images were segmented into gray matter, white matter, CSF, brainstem and cerebellum via the antsLongitudinalCorticalThickness.sh pipeline implemented in Advanced Normalization Tools (ANTs).⁵⁸ Parcellation for a region of interest (ROI) approach was performed via the Hammersmith Brain Atlas, containing 68 brain regions,⁵⁹ as well as VolBrain for the segmentation of subcortical regions.⁶⁰ For the current analysis, eight ROIs in the temporal lobe were preselected, of particularly high interest in AD: hippocampus (HPC), amygdala (AMG), medial anterior temporal lobe (M-ATL), lateral anterior temporal lobe (L-ATL), parahippocampal and ambient gyri (PHC), superior temporal gyrus (STG), middle and inferior temporal gyri (MTG/ITG) and fusiform gyrus (FFG). All brain volumetric data were normalized for the total intracranial volume (TIV) and averaged between both hemispheres.

Furthermore, T1-weighted and fluid-attenuated inversion recovery (FLAIR) MR images (TR = 9000 ms, TI = 2500 ms, TE = 79 ms, FA = 150°, 0.4 mm $\times$ 0.4 mm $\times$ 3 mm resolution) were used for the segmentation of white matter lesions in VolBrain, resulting in the total lesion volume of all intracerebral lesions at baseline and after intervention.^{61,62}

For whole-brain group comparison, a tensor-based-morphometry analysis was performed. The logarithm of the determinant of the Jacobians ($\text{Log}(\nabla\text{Jac})$), which represent local expansions or contractions in each voxel of each individual T1-weighted image when normalized to the subject template (created by the *antsLongitudinalCorticalThickness-pipelines*) were used to analyze structural changes. The difference of the logarithms of the determinants of the Jacobians corresponding to the follow-up and baseline images, respectively, were normalized to the OASIS template of miccai2012-multi-atlas-challenge-data,⁶³ and smoothed ($\sigma = 2$ mm) for consequent group analysis.

Statistical data analysis

Statistical analyses were performed using IBM SPSS Statistics 26 software and MATLAB R2019b. First, all data were visually inspected for normal distribution and possible outliers in boxplots and scatter plots. MR data were checked for segmentation failure, movement artifacts, and structural brain lesions as well. Pairwise deletion was applied for missing data. The participants' characteristics and measurement data were compared for group differences using mean (M), standard deviation (SD), median (*Mdn*), median absolute deviation (MAD) as well as independent samples t-test, Mann-Whitney-U-test and Chi-square analysis, as indicated. Correlation analyses of fitness and activity data were performed using Pearson's correlation and Spearman's rank correlation, reporting the correlation coefficients r and ρ , respectively. Differences between follow-up minus baseline values ($T_3 - T_1$) for the different assessment parameters were calculated and indicated with delta (Δ). Changes in fitness parameters were analyzed via multiple linear regression analysis, including group, fitness baseline levels, age, and sex as predictors, considering collinearity tests. To investigate the influence of the COVID-19 study protocol changes, a categorical variable (encoding 0 = not affected, 1 = affected), further referred to as $\text{Cov-19}_{\text{adj}}$, was entered into the model as well.

Prediction of neuropsychiatric, cognitive, and brain structural changes was then carried out via multiple linear regression analysis. Changes in VO_2max , i.e., $\Delta\text{VO}_2\text{max}$, and activity via Fitbit step count were entered as predictors in separate models. At first instance, we tested for potential confounding factors, including age, sex, baseline cognition, CSF status and study site as covariables in the model. Based on the results of this analysis, the design was simplified by excluding non-significant covariables for the final analysis, which was performed in each group separately regarding $\Delta\text{VO}_2\text{max}$ as the dependent variable, and in the overall cohort regarding the Fitbit step count. The influence of ATN and *APOE4* carrier status was further investigated by additionally entering those parameters as categorical variables into the regression models (encoding 0 = A^+T^- , 1 = A^+T^+ , as well as 0 = heterozygous *APOE4* allele

carrier/non-*APOE4* allele carrier, 1 = homozygous *APOE4* allele carrier) on a probatory basis.^{64–66} For neuropsychiatric and cognitive parameters, the respective baseline level was included in all models to adjust for the individual clinical disease manifestation. If the model included more than one possible predictor, the best fit was determined via changes in RMSE and R^2 as well as overall significance in all models. Significance is determined by an uncorrected $p < 0.05$ to meet the exploratory concept of the analysis. Effect size estimates were calculated using Cohen's d and Pearson's r as indicated. The 95% confidence intervals (95% CI) are reported. Furthermore, for the whole brain analysis, a voxel-wise permutation analysis ($n = 2000$ permutations) for comparison of the intervention and the control group was performed in BROCCOLI,⁶⁷ on voxels inside the brain tissue mask with a statistical threshold of $p < 0.05$, including MoCA at baseline, VO_2max at baseline, and education in years as covariates into the model.

Results

Participant flow

A total of 46 participants were initially included at baseline and randomized into either the intervention group ($n = 26$) or the control group ($n = 20$). At the UKA site, 19 people participated in the sports program, and seven in Simmerath. 43 participants completed the three-month and 43 completed the six-month follow-up (see Figure 1). Participants who missed all exercise sessions or psychoeducational lectures, yet still participated at least at the T_1 and T_3 assessments ($n = 3$) remained in the final analysis. Apart from that, one participant originally randomized to the intervention group, but unable to participate in any training session due to urinary incontinence and therefore sedentary, yet regularly attending the psychoeducational lectures, was allocated to the control group for final analysis. Furthermore, two participants of the intervention group were excluded from the final analysis for non-adherence to the home-based exercise program during the COVID-19 lockdown (German lockdown 03/19/2020 to 05/12/2020). Brain MRI was omitted in four out of the 41 remaining participants ($n = 1$ intervention group, $n = 3$ from control group) from at least one assessment time point. Reasons for not performing the MRI on these subjects were claustrophobia ($n = 3$), and the presence of a cardiac pacemaker unit ($n = 1$). For a detailed illustration of the participant flow, see also Figure 1.

Adherence to protocol

Mean adherence to the supervised exercise intervention was 72% (SD = 16%) and could be increased to 76% (SD = 16%) including two additional appointments that were offered if

attendance was below the targeted 80% after 26 weeks of intervention. Eleven participants of the intervention group (50%) had an attendance of more than 80%. Reasons for reducing training participation for longer than a week were chronic musculoskeletal pain ($n=5$), rehabilitation after minor surgery ($n=3$), respiratory infection ($n=2$) and a toe abscess ($n=1$).

Participants of the intervention group attended an average of four out of the seven psychoeducation lectures offered during the intervention period, while those in the control group attended an average of five events.

Regarding the activity diary, an average of 85% (SD = 22%) versus 77% (SD = 36%) of diary entries were completed, based on 182 days (26 weeks), in the intervention and the control group, respectively.

Occurrence of adverse events

There were no severe adverse events to report in both groups. Non-serious adverse events possibly associated with the intervention during the supervised exercise mainly included musculoskeletal pain ($n=4$), vertigo ($n=2$), nausea ($n=1$), arterial hypertension ($n=1$), and headache ($n=1$). In case of discomfort, the exercise load was reduced, or the training session was terminated

prematurely, which occurred once for three subjects and twice for one subject over the course of the intervention.

Baseline results and patient characteristics

An overview of the baseline characteristics and measurements of the analyzed study sample is given in Table 1A and 1B. At baseline, there was a group difference between the intervention group compared to the control group in terms of mean years in education (12.5 ± 3.8 years versus 14.8 ± 2.4 ; $U=107$, $z=-2.71$, 95% CI (1.00, 4.00), $p=0.01$, $r=0.42$) and mean MoCA score (17.1 ± 4 versus 21.3 ± 4.8 ; $t(39)=-3.02$, 95% CI (-6.89, -1.36), $p<0.01$, $ldl=0.95$). Performance in the executive functions domain also differed between the intervention and the control group (-0.21 ± 0.61 versus 0.24 ± 0.6 ; $t(39)=-2.41$, 95% CI (-0.84, -0.07), $p=0.02$, $ldl=0.75$). There were no group differences at baseline in other cognitive domains. Furthermore, the amyloid- β 42/40-ratio as well as tau and phospho-tau levels from CSF differed between both groups. However, it is important to note that CSF markers were acquired during the diagnostic process and not at the time point of study inclusion, with a maximum time distance of 1954 days before the intervention start. Therefore, interpretation of these differences in CSF pathology must be made with caution.

Table 1A. Basic characteristics of the included study sample ($n=41/46$) at baseline.

	Intervention Group ($n=22$)	Control Group ($n=19$)	p
Intervention Site (AC/SI)	15/7	15/4	0.438
Age (y)	72.1 (5.8)	68 (8.2)	0.067
Sex (m/f)	13/9	12/7	0.790
Education (y)	12.5 (3.8)	14.8 (2.4)	0.007*
Disease duration (y)	3.6 (2.2)	3.4 (1.7)	0.936
CDR	0.8 (0.3)	0.6 (0.4)	0.151
CSF Amyloid- β 1–42 (pg/ml) ^a	402.3 (161.7)	430.4 (176.8)	0.693
CSF Amyloid- β 42/40-ratio ^a	0.4 (0.1)	0.7 (0.9)	0.013*
CSF Tau (pg/ml) ^a	735.9 (322.7)	446.4 (263.2)	0.005*
CSF Phospho-Tau (pg/ml) ^a	98 (36.5)	70 (27.8)	0.011*
A ⁺ T ⁺ ; 2018, Jack et al. (%)	77.3	63.2	0.322
APOE4 Status (hetero-/homozygous, %)	40.9/22.7	63.2/10.5	0.333
Dementia medication (%) ^b	72.7	47.4	0.097
Psychiatric medication (%) ^c	31.8	31.6	0.987
Changes in dementia medication (%) ^d	31.8	36.8	0.735
Cardiovascular risk ^e	1.6 (1)	1.3 (1)	0.155

Frequencies are indicated for categorical variables, mean values and standard deviations for metric variables, respectively. * $p<0.05$. Missing values: CSF Amyloid- β 1–42 ($n=4$), CSF Amyloid- β 42/40-ratio ($n=5$); CSF Tau ($n=3$); CSF Phospho-Tau ($n=3$). AC, Aachen; SI, Simmerath; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; APOE4, Apolipoprotein E4

^aLab-specific AD-relevant cut-off values for cerebrospinal fluid parameters are as follows: amyloid- β 1–42 <450 pg/ml, amyloid- β 42/40-ratio <0.5, tau >450 pg/ml, phospho-tau >61 pg/ml, analysis was performed in the Neurochemical Laboratory at the University of Göttingen.^{82,83} One participant had the liquor diagnostics performed in an external practice, with a deviating lab-specific cut-off for amyloid- β 1–42 of <500 pg/ml.

^bIncluding the substances Donepezil, Rivastigmine, Galantamine, and Memantine licensed for the treatment of AD in Germany.

^cIncluding all kinds of psychopharmaceuticals such as antipsychotic, antidepressant or anxiolytic medication.

^dIndicated the change in dementia medication during the course of the intervention.

^e1 point each was assigned for the presence of arterial hypertension (anamnestic or medication), diabetes mellitus (anamnestic or medication), hypercholesterinemia (>5.16 mmol/L as the UKA internal laboratory reference value or medication), elevated body mass index (>30 kg/m²), active smoking (anamnestic); max. score = 5.²⁰

Table 1B. Measurement results at time points T₁ and T₃. Mean values and standard deviations, as well as group tests in direct time-point comparison, are indicated.

	Time point T ₁ (Baseline)			Time point T ₃		
	Intervention Group (n = 22)	Control Group (n = 19)	P	Intervention Group (n = 22)	Control Group (n = 19)	p
Fitness assessment						
VO ₂ max (ml/min/kg)	29.8 (4.72)	29.8 (6.17)	1.00	31.84 (4.12)	30.35 (5.55)	0.32
6-MWT (m)	532.32 (104.73)	532.92 (83.92)	0.98	533.83 (95.27)	547.01 (71.91)	0.63
Handgrip strength, dominant hand (kg)	30.68 (9.68)	30.84 (10.3)	0.96	31.02 (12.11)	32.82 (11.26)	0.63
Postural Stability (Z-score)	-0.03 (0.51)	0.03 (0.6)	0.78	0.04 (0.44)	-0.03 (0.58)	0.45
BMI (kg/m ²)	23.78 (3.2)	24.31 (2.89)	0.58	23.57 (3.1)	23.97 (2.95)	0.68
Cognitive performance						
MMSE	24.09 (3.16)	25.05 (3.6)	0.37			
MoCA	17.14 (3.97)	21.26 (4.78)	<0.01*	16.23 (3.9)	21.32 (5.21)	<0.01*
Attention (Z-score)	-0.16 (0.76)	0.19 (0.65)	0.08	-0.22 (0.79)	0.05 (0.78)	0.33
Verbal memory (Z-score)	-0.12 (0.44)	0.14 (0.53)	0.09	0.06 (0.60)	0.12 (0.57)	0.78
Executive functions (Z-score)	-0.21 (0.61)	0.24 (0.6)	0.02*	-0.25 (0.53)	0.22 (0.53)	<0.01*
Neuropsychiatric symptoms						
QoL (patient)	37.27 (4.59)	37 (5.31)	0.60	36.91 (4.77)	35 (4.49)	0.31
QoL (family)	35.5 (3.82)	34.16 (6.88)	0.33	33.86 (4.79)	34.22 (4.4)	0.79
HADS (total score)	6.59 (5.8)	9.16 (6.88)	0.20	9.27 (5.93)	11 (9.82)	0.51
NPI-10	7.72 (6.31)	7.19 (10.09)	0.34	7.86 (9.68)	7.56 (14.8)	0.31
PSQ-I	4.36 (3.47)	5.58 (3.79)	0.29	4.27 (3.53)	3.89 (2.33)	0.90
MRI						
Hippocampus Volume (%TIV)	0.22 (0.03)	0.23 (0.04)	0.48	0.22 (0.03)	0.23 (0.04)	0.32
Gray Matter Volume (%TIV)	34.19 (1.42)	34.95 (2.44)	0.24	33.82 (1.47)	34.6 (2.75)	0.31
Cortical Thickness (mm)	2.61 (0.12)	2.7 (0.23)	0.16	2.55 (0.14)	2.66 (0.25)	0.12
White Matter Volume (%TIV)	30.92 (1.78)	30.75 (1.54)	0.76	30.89 (1.87)	31.02 (2)	0.84
White Matter Lesion Volume (%TIV)	0.46 (0.7)	0.42 (0.63)	0.19	0.54 (0.75)	0.43 (0.64)	0.10

*p < 0.05. Missing values: T₁, postural stability (n = 1), Quality of Life (family) (n = 2), NPI-10 (n = 7), all MRI parameters (n = 4); T₃, 6-MWT (n = 1), Verbal Memory (Z-score) (n = 1), Quality of Life (patient) (n = 1), Quality of Life (family) (n = 1), NPI-10 (n = 2), all MRI parameters (n = 4). VO₂max: maximal oxygen uptake; 6-MWT: 6-Minute Walk Test; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; HADS: Hospital Anxiety and Depression Scale; TIV: total intracranial volume.

Monitoring of physical activity and fitness during the intervention

Assessment and monitoring of physical activity served mainly two purposes: (1) to check for protocol adherence, and (2) to assess general physical activity and fitness during the study. In a recent publication, we demonstrated the good validity of the diary and fitness trackers for the assessment of physical activity and fitness in the same patient group,³⁸ with comparable values in MET-scores and MVPA between the assessment via the fitness tracker and the diary (see Supplemental Table 3 and Supplemental Figure 1). Therefore, fitness tracker activity levels were considered as representative for general activity level for the whole intervention period, while physical activity reported by the PAQ50+ questionnaire was used as an assessment prior to intervention start.

Based on the physical activity reported in the diaries, both the intervention and the control group fulfilled, on average, the current WHO recommendations for general physical activity for the elderly during the study period, with a median weekly activity time of 171 min of moderate-intensity and

91 min of vigorous activity in the intervention group, and 281 min of moderate-intensity and 72 min of vigorous activity in the control group per week.¹⁷ At the subject level, the WHO recommendation was achieved by 19 participants in the intervention group and 16 participants in the control group.

Over the six-month intervention period, the global level of daily MET derived from the diary remained constant over time in both groups. The rate of vigorous activity reported was higher in the intervention group compared to the control group (intervention, *Mdn* = 15.18, *MAD* = 3.50; control, *Mdn* = 10.39, *MAD* = 6.87; *U* = 112, *z* = -2.13, 95% CI (-11.93, -0.57), *p* = 0.03, *r* = 0.34). However, the rate of moderate activity appeared to be higher in the control group compared to the intervention group (see also Figure 3), where we observed that a few outlying individuals in the control group with an exceptionally high activity level led to a generally higher level of reported moderately intense activity on average (intervention, *Mdn* = 27.39, *MAD* = 12.94; control, *Mdn* = 48.19, *MAD* = 20.25; *U* = 86, *z* = -2.86, 95% CI (6.99, 41.60), *p* < 0.01, *r* = 0.46).

The development of fitness parameters over the intervention is illustrated in Figure 4: all fitness parameters increased in the

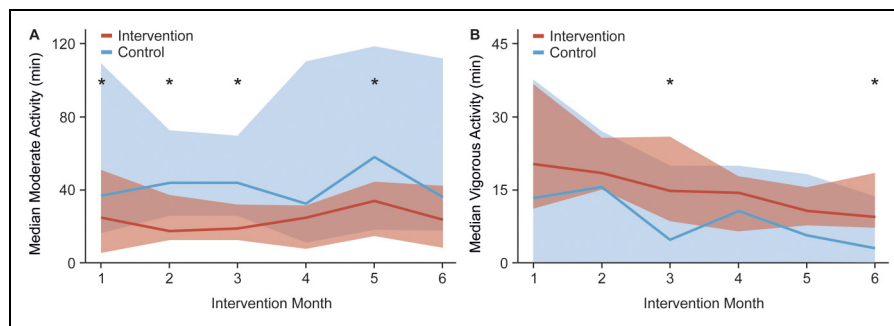


Figure 3. Physical activity development during the intervention period derived from the paper-based physical activity diary. Daily median moderate (A) and vigorous (B) activity minutes for every intervention month in both groups are indicated, including the 95% confidence intervals. For the intervention group, the supervised exercise program and all home sports activities are included. *significant results in the Mann-Whitney U test with $p < 0.05$. Missing values: $n = 2$.

intervention group. Compared to the control group, however, only VO_2max (intervention, $M_{T3-1} = 2.04$, $SD = 2.34$; control, $M_{T3-1} = 0.55$, $SD = 2.57$) and the postural stability score (intervention, $M_{T3-1} = 0.1$, $SD = 0.41$; control, $M_{T3-1} = -0.06$, $SD = 0.45$) improved in the intervention group.

We then analyzed which factors positively predicted $\Delta\text{VO}_2\text{max}$ in multiple linear regression analyses. As expected, $\Delta\text{VO}_2\text{max}$ was significantly associated with an affiliation to the intervention group ($t = 2.52$, $p = 0.02$), furthermore with an increase of activity compared to before the intervention start as reflected by $\Delta\text{PAQ50} + T_{2/3-1}$ ($t = 2.07$, $p = 0.05$), and a lower baseline VO_2max ($t = -3.59$, $p < 0.01$) (see Figure 5). Regarding the additional fitness parameters, there were no group differences revealed in the regression analyses. A summary of all statistical models is available in Supplemental Table 4.

No significant change was detected in the general activity levels, measured by diary MET, of participants affected by changes to the study protocol during the COVID-19 pandemic ($z = -1.34$, 95% CI $(-3.08, 0.57)$, $p = 0.26$, $r = 0.28$), compared to those who were not affected. Furthermore, multiple regression analysis revealed no influence of the COVID-19 adjustment variable ($\text{Cov-19}_{\text{adj}}$) on development of VO_2max , 6-MWT distance, and postural stability, leading to its subsequent exclusion from the models. However, a certifiable beneficial effect on the development of handgrip strength could be reported for people being affected by the COVID-19 protocol changes ($t = 2.35$, $p = 0.03$). None of the participants in the exercise group presented clinical symptoms or were tested positive for COVID-19 during their six-month intervention period.

Influence of physical activity and fitness development on changes in neuropsychiatric symptoms, cognitive performance, and brain integrity

As mentioned before, baseline VO_2max showed a negative association with $\Delta\text{VO}_2\text{max}$ ($r = -0.44$, 95% CI $[-0.66$,

$-0.15]$, $p < 0.01$) and was therefore initially regressed out from further analyses, applying the unstandardized residuals of $\Delta\text{VO}_2\text{max} \sim \text{VO}_2\text{max}_{T1}$ in subsequent regression analyses. Since both groups revealed differences in cognitive and educational status and potentially in the neurodegenerative markers from CSF at baseline, and to circumvent that baseline imbalances potentially hampered direct group comparisons (see Table 1B), we performed multiple linear regression analyses for disease outcome parameters separately in both groups. After screening the covariables, only the respective baseline levels of neuropsychiatric and cognitive parameters, showing a significant modifying effect, remained in the model; all other covariables were subsequently excluded to simplify the analysis. Interestingly, only in the intervention group CRF improvement did positively predict changes in MoCA ($\text{RMSE} = 2.48$, $p = 0.03$, $R^2_{\text{adj}} = 0.25$) and in executive functions ($\text{RMSE} = 0.26$, $p < 0.01$, $R^2_{\text{adj}} = 0.45$), as well as in volumetric changes of regions of the temporal lobe (HPC, $\text{RMSE} = 4 \times 10^{-3}$, $p = 0.04$, $R^2_{\text{adj}} = 0.16$; AMG, $\text{RMSE} < 0.01$, $p = 0.03$, $R^2_{\text{adj}} = 0.20$; M-ATL, $\text{RMSE} = 0.01$, $p = 0.01$, $R^2_{\text{adj}} = 0.28$; PHC, $\text{RMSE} = 0.01$, $p = 0.01$, $R^2_{\text{adj}} = 0.25$; STG, $\text{RMSE} = 0.01$, $p = 0.05$, $R^2_{\text{adj}} = 0.15$), which was not the case for the control group, indicating an isolated mediating positive role of $\Delta\text{VO}_2\text{max}$ on these outcome parameters in the intervention group (Figure 6A, B). In models that considered changes in neuropsychiatric and cognitive parameters, an inverse association was found between the baseline levels of these parameters and their changes from baseline to T3 (T_{3-1} deltas). Furthermore, neither the A^+T^+ status nor the $APOE4$ carrier status played a moderating role in either group, which led to their exclusion from the analysis models.

As a second step, the influence of the physical activity level derived from Fitbit step count was analyzed on the outcome parameters, as this was shown to be the generally most reliable measurement of the Fitbit tracker in previous studies.^{68,69} Since mean activity levels via Fitbit recordings were similar between groups, we hypothesized that the

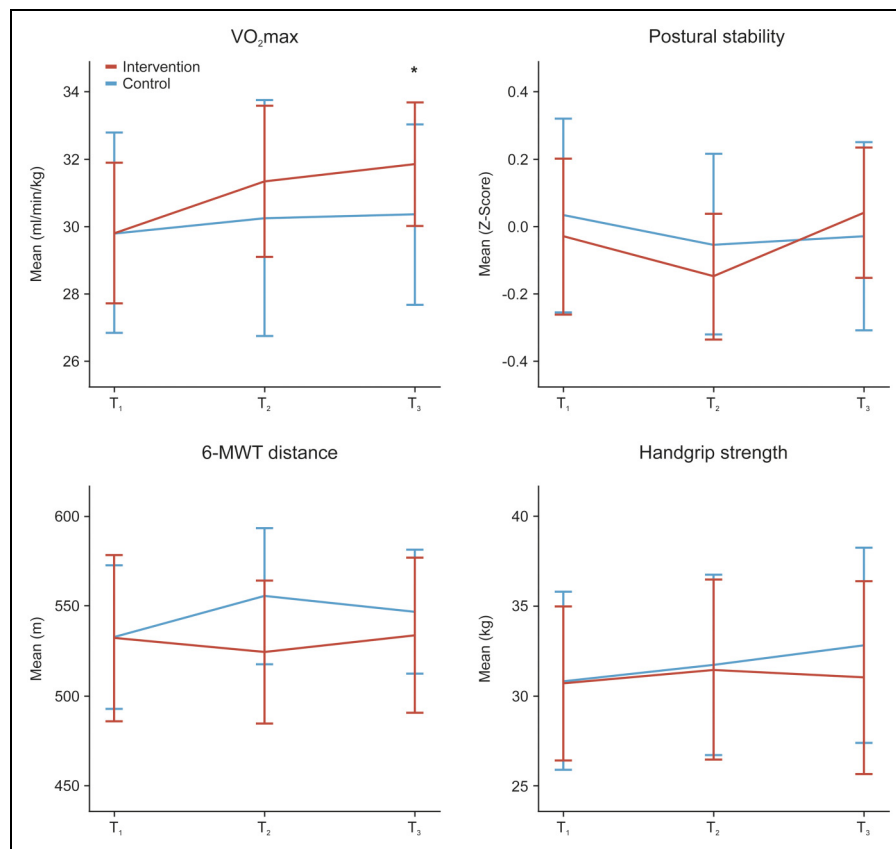


Figure 4. Development of fitness parameters assessed at all three visits (at baseline T₁, T₂, and T₃) in both groups. Mean values are indicated, including the 95% confidence intervals, significant group difference in $\Delta\text{VO}_2\text{max}$ in multiple linear regression analysis with $p = 0.02$, considering baseline VO_2max and $\Delta\text{PAQ50+}$ as covariables (see also Figure 5). There were no significant group differences concerning the other fitness parameters.

influence of physical activity itself might differ from the immediate intervention effect reflected by the CRF improvement. Supporting this assumption, a small to moderate positive association was found between the Fitbit step count as the absolute physical activity level and baseline VO_2max ($\rho = -0.37$, 95% CI (0.05, 0.62), $p = 0.02$), but not $\Delta\text{VO}_2\text{max}$ ($\rho = -0.15$, 95% CI (-0.45, 0.18), $p = 0.36$). Again, multiple linear regression analyses were performed to analyze the influence of physical activity via Fitbit step count on disease outcome parameters in the overall cohort ($n = 39$) (Figure 6C). Higher physical activity levels were associated with an increased Quality of Life for caregivers (RMSE = 3.53, $p = 0.01$, $R^2_{\text{adj}} = 0.23$), as well as better performance in executive functions (RMSE = 0.31, $p < 0.01$, $R^2_{\text{adj}} = 0.27$). Again, there was a negative association with the baseline levels of these variables. There was also a positive effect of the Fitbit step count on the regional cortical thickness of the lateral anterior temporal gyrus (RMSE = 0.18, $p = 0.03$, $R^2_{\text{adj}} = 0.11$). No influence of $\Delta\text{VO}_2\text{max}$ was observed on vascular lesion change, sleep, and neuropsychiatric and depressive symptoms from NPI and HADS. See Supplemental Table 5 for further details on the analyses.

Whole-brain analysis revealed higher brain volume in the intervention group in the upper frontal brain lobe compared to the psychoeducation control group when taking MoCA and VO_2max baseline levels, as well as education, as covariates into account at a liberal cluster threshold of $p < 0.1$ with $n = 2000$ permutations. There were no significant group clusters at a cluster threshold of $p < 0.05$ (see Figure 7).

Discussion

This study presents the results of activity and fitness development from the Dementia-MOVE trial, a six-month multi-component exercise intervention in AD. We examined the influence of CRF and physical activity on different clinical aspects of AD pathology, such as neuropsychiatric symptoms, sleep, quality of life, cognitive performance, as well as structural cerebral changes assessed by 3T MRI.

The physical activity and fitness assessment methods used in our study demonstrated high compliance with our protocol instructions, adhering to the current WHO recommendations on weekly activity rates for the elderly.¹⁷ The physical activity assessment via wearable fitness trackers

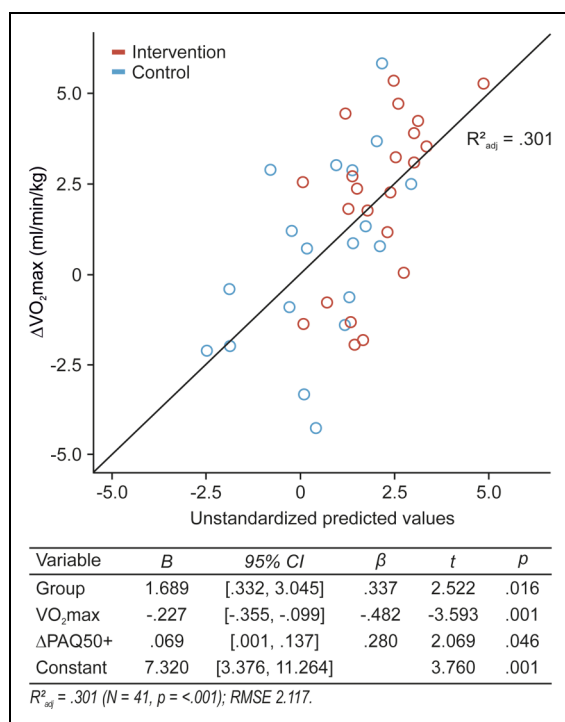


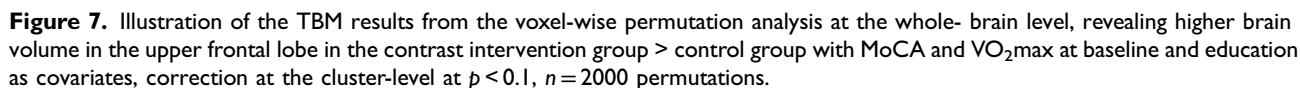
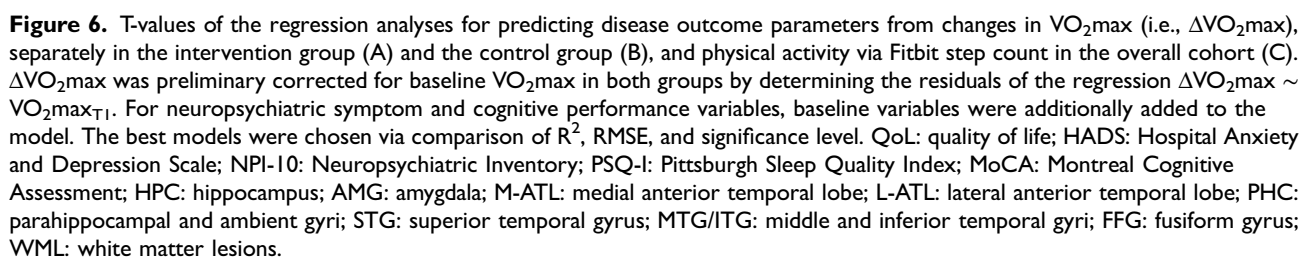
Figure 5. Multiple linear regression model of Δ VO₂max. The unstandardized predicted values of the model, including group, baseline VO₂max, and Δ PAQ50+ as significant predictors are plotted on the x-axis against Δ VO₂max on the y-axis. Colors indicate data points of the intervention group in red and data points of the control group in blue, respectively. The model summary is included below, indicating the regression coefficient B, its 95% confidence interval (95% CI), the standardized regression coefficient β , the respective t value, and the significance level p for each predictor, as well as the overall model accuracy, including the effect size R^2_{adj} , p, and root mean squared error (RMSE). The significance level is defined as $p < 0.05$.

showed comparable physical activity levels between the intervention and the control group. However, the written diary revealed differences, particularly in the reporting of moderate activity levels. It, therefore, cannot be entirely ruled out that participants in the control group were more diligent and detailed in keeping the diary, especially when referring to moderate activities, compared to the intervention group, which might have focused more on the intensive training and its reporting. One might further argue that a difference in the cognitive state of the control group at baseline might lead to better activity reporting in the diaries in the control group. However, our findings did not show an association between cognitive state, as represented by the MoCA score, and compliance in keeping the diary in our sample.

We further analyzed the association between physical activity and CRF, represented by VO₂max. As expected, high activity levels derived from the Fitbit were positively associated with VO₂max from baseline, but not with

Δ VO₂max. Interestingly, participants with lower baseline CRF levels who successfully increased their physical activity levels, as indicated by the Δ PAQ50+_{T2/3-1} score, benefited the most from our multicomponent intervention program. They increased their VO₂max, which had a positive effect on various AD progress parameters, including a positive mediating effect on regional brain structure and cognitive performance. Therefore, it can be assumed that, although there is a detectable positive influence of increased physical activity on CRF development, the individual baseline activity level must be considered separately concerning its influence on AD progression.^{14,70} CRF improvement itself, reflected by an increase in VO₂max, was positively associated with an affiliation to the intervention group validating the effectiveness of our structured training concept for improving fitness in a sample of elderly and cognitively impaired participants. This aligns with previous findings emphasizing that increased physical activity is a crucial element to improve CRF, yet conveying its greatest effect through organized and regular training sessions of especially vigorous intensity,^{71,72} which, regardless of the average activity level, was only ensured in our intervention group. It could therefore be inferred that a specific level of activity at a specific intensity level is regularly required to produce benefits. This is underlined by the results of the intervention group, which showed a higher rate of activity on a vigorous level, while the control group engaged at a more moderate activity level, not revealing a significant impact. A positive trend was also reported regarding the development of postural stability, a domain that was actively trained in our program, which should be recommended even apart from its sheer effect on AD progression as an important preventive measure to reduce the risk of falls.⁷³ On the other hand, there was no remarkable response in other fitness parameters that were not specifically addressed in our intervention program, such as handgrip strength and the 6-MWT distance. A beneficial effect of the COVID-19 protocol changes on development of handgrip strength can probably be explained by training adjustments to home-based and space-restricted training forms with a focus on single muscle groups during the lockdown.

We further analyzed how VO₂max improvement and average activity levels influenced AD outcome parameters. A modifying beneficial effect of CRF improvement was only observed in the intervention group that successfully increased VO₂max over the course of the intervention period, supporting previous findings that demonstrated an effect of exercise-induced CRF increase on cognitive performance and AD-affected brain regions of the temporal lobe. This effect could be related to a combination of reduced brain inflammation, higher brain reserve, and reduced brain damage in terms of reduced vascular, neurotoxic, or oxidative stress,⁷⁴ leading to a reduced cellular loss and, therefore, maintained brain volumes and cortical



levels as non-specific progress markers for neuropsychiatric and cognitive parameters suggest that clinically more severely affected individuals of our sample were able to benefit more from the intervention in combination with their thereby achieved fitness improvement.^{64,76} However,

there was no clear beneficial effect of CRF improvement on neuropsychiatric symptoms which has been reported in previous studies.^{77,78} In contrast, we found higher activity levels associated with increased quality of life for caregivers, highlighting another quality sign of multicomponent intervention concepts, by effectively relieving caregivers and offering space for discourse of likewise affected people and their relatives, even if this effect was not significantly reflected by the participants themselves.⁷⁹ Not only CRF, but also high physical activity led to a beneficial effect on the executive functions in the overall sample, pointing out that not only CRF increase but also physical activity on a regular base itself contributes to a positive development of cognitive performance in AD. This beneficial effect on executive functions is also reflected on the brain level, where our brain voxel-wise permutation analysis points at positive volume effects in frontal brain regions in trend. Recent research has pointed to an assumed predominant effect of multicomponent exercise on executive functions which is also in line with our cerebral findings of effects in the frontal lobe.⁸⁰ There was no beneficial effect of physical activity and CRF on vascular lesions, which one would assume given the positive mediating influence of these factors on the cardiovascular risk profile.⁶² However, it might be the case that the intervention period of six months is too short to observe large effects in vascular changes on the cerebral level but would rather be observed on long-term outcomes.

In conclusion, we demonstrated that our multicomponent exercise intervention design can be an effective method to improve CRF in a sample of people affected with AD, especially for those with previously low fitness levels after six months of intervention. VO_2max improvement was associated with advantageous developments in cognitive performance and a positive mediating effect on brain structure in AD-relevant regions of the temporal lobe in the intervention group, while negative associations with cognitive baseline levels suggest a higher benefit for people with more cognitive impairment. Furthermore, we found high levels of physical activity to be associated with increased cognitive performance, sustained cortical thickness in the temporal lobe area, and higher quality of life in caregivers of AD-affected individuals, marking another crucial domain to reduce the disease burden through physical interventions.

Even though there was a randomization process before group allocation, group differences occurring at baseline in single assessment parameters are inevitable, and our intervention group may have been more strongly affected by AD pathology based on their initial CSF status at the time of diagnosis and cognitively more impaired and with a lower cognitive reserve compared to the control group, pointing to differences in the MoCA score, the executive function, and the education level at baseline. This was taken into account in our statistical analyses, and we excluded a significant influence of these potential confounding factors on the outcome parameters. Still, this aspect has to be considered when looking at absolute

outcome parameters beyond the change from pre- to post-intervention state alone. As suggested by previous publications, it is presumably challenging to account for all potential confounding factors during a temporary intervention, which may influence the outcomes and hinder direct comparisons between groups. In addition, we encountered minor fluctuations in protocol adherence due to medical issues related not only to the underlying disease but also expected in interventions involving an older population. Furthermore, necessary adjustments to the protocol were required during the COVID-19 lockdown. Nevertheless, a strong point of the present sample is the very detailed clinical characterization, which is often lacking in previously reported studies.¹¹ Considering the current body of research and the mentioned limitations, which are common in interventional research, our study demonstrates the positive influence of both physical activity and fitness improvement on AD pathology. The underlying effects on the cerebral level should be considered multifactorial and will need to be the subject of preclinical and clinical intensive research in the future.⁸¹ Our study provides an important gain in knowledge on the rarely considered relationship between fitness and physical activity, both of which should be taken into account according to our study results. The present study has a limited sample size, which was based on initial power analyses related to our primary outcome parameter (see also⁶²). However, it can support the design of future intervention studies, which should also include well-characterized samples, as in the present study, and additionally incorporate larger sample sizes, longer intervention periods, and long-term follow-ups to enable subgroup analyses and compensate for group differences that might influence the outcomes, particularly concerning baseline cognition, fitness, activity levels, and differences in AD pathology, which might influence the distinct response to intervention effects.

According to our findings, which show a positively mediating influence of cardiovascular fitness and physical activity on several disease outcome parameters in AD, regular, structured exercise and activity increase in people affected by AD should be aimed at, both for primary and secondary prevention. Additionally, the intensity of physical activity must always be considered. Connection to professional, multicomponent training programs should be established early in the disease, but it is also highly effective for people with advanced disease manifestations, as shown in our study, and is therefore never too late.

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Statements and declarations

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Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

The data supporting the findings of this study are available on reasonable request from the corresponding author.

Supplemental material

Supplemental material for this article is available online.

References

1. Prince MJ, Wimo A, Guerchet MM, et al. *World Alzheimer Report 2015. The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends*. London, UK: Alzheimer's Disease International, 2015.
2. Gustavsson A, Norton N, Fast T, et al. Global estimates on the number of persons across the Alzheimer's disease continuum. *Alzheimers Dement* 2023; 19: 658–670.
3. Crous-Bou M, Minguillón C, Gramunt N, et al. Alzheimer's disease prevention: from risk factors to early intervention. *Alzheimers Res Ther* 2017; 9: 71.
4. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet* 2015; 385: 2255–2263.
5. Morris JK, Vidoni ED, Johnson DK, et al. Aerobic exercise for Alzheimer's disease: a randomized controlled pilot trial. *PLoS One* 2017; 12: e0170547.
6. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 2020; 396: 413–446.
7. Hersi M, Irvine B, Gupta P, et al. Risk factors associated with the onset and progression of Alzheimer's disease: a systematic review of the evidence. *Neurotoxicology* 2017; 61: 143–187.
8. López-Ortiz S, Pinto-Fraga J, Valenzuela PL, et al. Physical exercise and Alzheimer's disease: effects on pathophysiological molecular pathways of the disease. *Int J Mol Sci* 2021; 22: 2897.
9. Thomas BP, Tarumi T, Sheng M, et al. Brain perfusion change in patients with mild cognitive impairment after 12 months of aerobic exercise training. *J Alzheimers Dis* 2020; 75: 617–631.
10. Sinha N, Berg CN, Yassa MA, et al. Increased dynamic flexibility in the medial temporal lobe network following an exercise intervention mediates generalization of prior learning. *Neurobiol Learn Mem* 2021; 177: 107340.
11. Haeger A, Costa AS, Schulz JB, et al. Cerebral changes improved by physical activity during cognitive decline: a systematic review on MRI studies. *Neuroimage Clin* 2019; 23: 101933.
12. Anderson-Hanley C, Barcelos NM, Zimmerman EA, et al. The Aerobic and Cognitive Exercise Study (ACES) for community-dwelling older adults with or at-risk for mild cognitive impairment (MCI): neuropsychological, neurobiological and neuroimaging outcomes of a randomized clinical trial. *Front Aging Neurosci* 2018; 10: 76.
13. Suzuki T, Shimada H, Makizako H, et al. A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment. *PLoS One* 2013; 8: e61483.
14. Dougherty RJ, Boots EA, Lindheimer JB, et al. Fitness, independent of physical activity is associated with cerebral blood flow in adults at risk for Alzheimer's disease. *Brain Imaging Behav* 2020; 14: 1154–1163.
15. Banerjee T, Peterson M, Oliver Q, et al. Validating a commercial device for continuous activity measurement in the older adult population for dementia management. *Smart Heal* 2018; 5–6: 51–62.

16. Borges-Machado F, Ribeiro Ó, Sampaio A, et al. Feasibility and impact of a multicomponent exercise intervention in patients with Alzheimer's disease: a pilot study. *Am J Alzheimers Dis Other Dement* 2019; 34: 95–103.
17. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med* 2020; 54: 1451–1462.
18. Coupé P, Tourdias T, Linck P, et al. Lesionbrain: an online tool for white matter lesion segmentation. In: International Workshop on Patch-based Techniques in Medical Imaging (MICCAI), Grenade, Spain, September 2018, pp.95–103.
19. Glenn J, Madero EN, Gray M, et al. Engagement with a digital platform for multimodal cognitive assessment and multidomain intervention in a Japanese population: pilot, quasi-experimental, longitudinal study. *JMIR mHealth UHealth* 2019; 7: e15733.
20. Haeger A, Costa AS, Romanzetti S, et al. Effect of a multicomponent exercise intervention on brain metabolism: a randomized controlled trial on Alzheimer's pathology (Dementia-MOVE). *Alzheimers Dement (N Y)* 2020; 6: e12032.
21. Jack CR, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018; 14: 535–562.
22. Haeger A, Bottlaender M, Lagarde J, et al. What can 7T sodium MRI tell us about cellular energy depletion and neurotransmission in Alzheimer's disease? *Alzheimers Dement* 2021; 17: 1843–1854.
23. Haeger A, Boumezbear F, Bottlaender M, et al. 3T Sodium MR imaging in Alzheimer's disease shows stage-dependent sodium increase influenced by age and local brain volume. *Neuroimage Clin* 2022; 36: 103274.
24. Abramson JH. WINPEPI Updated: computer programs for epidemiologists, and their teaching potential. *Epidemiol Perspect Innov* 2011; 8: 1.
25. Luxton N, Alison JA, Wu J, et al. Relationship between field walking tests and incremental cycle ergometry in COPD. *Respirology* 2008; 13: 856–862.
26. Epley B. Pounding chart. In: *Boyd epley workout*. Lincoln, NE: Body Enterprises, 1985, 1985, pp.86.
27. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982; 14: 377–381.
28. Wang S, Liu H-Y, Cheng Y-C, et al. Exercise dosage in reducing the risk of dementia development: mode, duration, and intensity-a narrative review. *Int J Environ Res Public Health* 2021; 18: 13331.
29. Bundeszentrale für gesundheitliche Bildung. Bewegungspackung. <https://shop.bzga.de/bewegungspackung-60582387> (accessed March 31, 2024).
30. Kivipelto M, Solomon A, Ahtiluoto S, et al. The Finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER): study design and progress. *Alzheimers Dement* 2013; 9: 657–665.
31. Albouaini K, Egred M, Alahmar A, et al. Cardiopulmonary exercise testing and its application. *Postgrad Med J* 2007; 83: 675–682.
32. Åstrand P-O and Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. *J Appl Physiol* 1954; 7: 218–221.
33. Ries JD, Echternach JL, Nof L, et al. Test-retest reliability and minimal detectable change scores for the timed “up & go” test, the six-Minute walk test, and gait speed in people with Alzheimer disease. *Phys Ther* 2009; 89: 569–579.
34. Rijk JM, Roos PR, Deckx L, et al. Prognostic value of handgrip strength in people aged 60 years and older: a systematic review and meta-analysis. *Geriatr Gerontol Int* 2016; 16: 5–20.
35. Raschner C, Lember S, Platzer H-P, et al. S3-Check - evaluation and generation of normal values of a test for balance ability and postural stability. *Sportverletz Sportschaden* 2008; 22: 100–105.
36. Ide R, Ota M, Hada Y, et al. Dynamic balance deficit and the neural network in Alzheimer's disease and mild cognitive impairment. *Gait Posture* 2022; 93: 252–258.
37. Shaughnessy KA, Hackney KJ, Clark BC, et al. A narrative review of handgrip strength and cognitive functioning: bringing a new characteristic to muscle memory. *J Alzheimers Dis* 2020; 73: 1265–1278.
38. David S, Hohenfeld C, Haberl L, et al. Physical activity monitoring in Alzheimer's disease during sport interventions: a multi-methodological perspective. *Front Neurol* 2023; 14: 1195694.
39. Huy C and Schneider S. [Instrument for the assessment of middle-aged and older adults' physical activity: design, reliability and application of the German-PAQ-50+]. *Z Gerontol Geriatr* 2008; 41: 208–216.
40. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000; 32: S498–S504.
41. Yu F, Mathiason MA, Han S, et al. Mechanistic effects of aerobic exercise in Alzheimer's disease: imaging findings from the pilot FIT-AD trial. *Front Aging Neuroscience* 2021; 13: 703691.
42. Van Blarigan EL, Kenfield SA, Tatum L, et al. The Fitbit One physical activity tracker in men with prostate cancer: validation study. *JMIR Cancer* 2017; 3: e5.
43. von Döbeln W, Astrand I and Bergström A. An analysis of age and other factors related to maximal oxygen uptake. *J Appl Physiol* 1967; 22: 934–938.
44. Burr JF, Bredin SSD, Faktor MD, et al. The 6-minute walk test as a predictor of objectively measured aerobic fitness in healthy working-aged adults. *Phys Sportsmed* 2011; 39: 133–139.
45. Logsdon RG, Gibbons LE, McCurry SM, et al. Assessing quality of life in older adults with cognitive impairment. *Psychosom Med* 2002; 64: 510–519.
46. Herrmann-Lingen C, Buss U and Snaith RP. *Hospital anxiety and depression scale: HADS-D; Deutsche Version; ein Fragebogen zur Erfassung von Angst und Depressivität in der somatischen Medizin; Testdokumentation und Handanweisung*. Huber, 2005.
47. Cummings JL, Mega M, Gray K, et al. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994; 44: 2308–2314.

48. Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; 28: 193–213.
49. Folstein MF, Folstein SE and McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–198.
50. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; 53: 695–699.
51. Zimmermann P and Fimm B. *Testbatterie zur Aufmerksamkeitsprüfung (TAP) Version 1.7*. Herzogenrath: PSYTEST Verlag, 2002.
52. Aste M, Neubauer A and Horn R. *Wechsler Intelligenztest fuer Erwachsene (WIE). Deutschsprachige Bearbeitung und Adaptation des WAIS- III von David Wechsler*. Frankfurt: Harcourt Test Services, 2006.
53. Niemann H, Sturm W, Thöne-Otto AIT, et al. *CVLT California Verbal Learning Test*. German adaptation. Manual.
54. Wagner S, Helmreich I, Dahmen N, et al. Reliability of three alternate forms of the Trail Making Tests A and B. *Arch Clin Neuropsychol* 2011; 26: 314–321.
55. Aschenbrenner S, Tucha O and Lange K. *Regensburg Word Fluency Test [Regensburger Wortflüssigkeits-Test (RWT)]*. Göttingen: Hogrefe, 2000.
56. Bäuml G. Farbe-Wort-Interferenztest (FWIT) nach J. R. Stroop.
57. Schmitz-Hübsch T, Fimmers R, Rakowicz M, et al. Responsiveness of different rating instruments in spinocerebellar ataxia patients. *Neurology* 2010; 74: 678–684.
58. Avants BB, Tustison NJ, Song G, et al. A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage* 2011; 54: 2033–2044.
59. Hammers A, Allom R, Koepp MJ, et al. Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. *Hum Brain Mapp* 2003; 19: 224–247.
60. Manjón JV and Coupé P. Volbrain: an online MRI brain volumetry system. *Front Neuroinform* 2016; 10: 30.
61. Romero J, Coupé P, Tourdias T, et al. LesionBrain: An online tool for white matter lesion segmentation.
62. Haeger A, Mangin J-F, Vignaud A, et al. Imaging the aging brain: study design and baseline findings of the SENIOR cohort. *Alzheimers Res Ther* 2020; 12: 77.
63. Open Access Series of Imaging Studies (OASIS). Retrieved from <https://www.oasis-brains.org> (accessed May 31, 2024).
64. Tokgöz S and Claassen JAHR. Exercise as potential therapeutic target to modulate Alzheimer's disease pathology in APOE ϵ 4 carriers: a systematic review. *Cardiol Ther* 2021; 10: 67–88.
65. Aslanyan V, Ortega N, Fenton L, et al. Protective effects of sleep duration and physical activity on cognitive performance are influenced by β -amyloid and brain volume but not tau burden among cognitively unimpaired older adults. *Neuroimage Clin* 2023; 39: 103460.
66. de Frutos-Lucas J, Frost N, Erickson KI, et al. Does APOE genotype moderate the relationship between physical activity, brain health and dementia risk? A systematic review. *Ageing Res Rev* 2020; 64: 101173.
67. Eklund A, Dufort P, Villani M, et al. BROCCOLI: software for fast fMRI analysis on many-core CPUs and GPUs. *Front Neuroinform* 2014; 8: 24.
68. Germini F, Noronha N, Borg Debono V, et al. Accuracy and acceptability of wrist-wearable activity-tracking devices: systematic review of the literature. *J Med Internet Res* 2022; 24: e30791.
69. Fuller D, Colwell E, Low J, et al. Reliability and validity of commercially available wearable devices for measuring steps, energy expenditure, and heart rate: systematic review. *JMIR mHealth UHealth* 2020; 8: e18694.
70. Lee D-C, Sui X, Ortega FB, et al. Comparisons of leisure-time physical activity and cardiorespiratory fitness as predictors of all-cause mortality in men and women. *Br J Sports Med* 2011; 45: 504–510.
71. Lakoski SG, Barlow CE, Farrell SW, et al. Impact of body mass index, physical activity, and other clinical factors on cardiorespiratory fitness (from the Cooper Center longitudinal study). *Am J Cardiol* 2011; 108: 34–39.
72. Zhang X, Li Q, Cong W, et al. Effect of physical activity on risk of Alzheimer's disease: a systematic review and meta-analysis of twenty-nine prospective cohort studies. *Ageing Res Rev* 2023; 92: 102127.
73. Dolatabadi E, Van Ooteghem K, Taati B, et al. Quantitative mobility assessment for fall risk prediction in dementia: a systematic review. *Dement Geriatr Cogn Disord* 2018; 45: 353–367.
74. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet* 2017; 390: 2673–2734.
75. Huang X, Zhao X, Li B, et al. Comparative efficacy of various exercise interventions on cognitive function in patients with mild cognitive impairment or dementia: a systematic review and network meta-analysis. *J Sport Heal Sci* 2022; 11: 212–223.
76. Brown BM, Peiffer J and Rainey-Smith SR. Exploring the relationship between physical activity, beta-amyloid and tau: a narrative review. *Ageing Res Rev* 2019; 50: 9–18.
77. Chen KM, Kuo CC, Chang YH, et al. Resistance band exercises reduce depression and behavioral problems of wheelchair-bound older adults with dementia: a cluster-randomized controlled trial. *J Am Geriatr Soc* 2017; 65: 356–363.
78. Liu Q, Ni W, Zhang L, et al. Comparative efficacy of various exercise interventions on depression in older adults with mild cognitive impairment: a systematic review and network meta-analysis. *Ageing Res Rev* 2023; 91: 102071.
79. Song D and Yu DSF. Effects of a moderate-intensity aerobic exercise programme on the cognitive function and quality of life of community-dwelling elderly people with mild cognitive impairment: a randomised controlled trial. *Int J Nurs Stud* 2019; 93: 97–105.
80. Yan J, Li X, Guo X, et al. Effect of multicomponent exercise on cognition, physical function and activities of daily life in older adults with dementia or mild cognitive impairment: a

- systematic review and meta-analysis. *Arch Phys Med Rehabil* 2023; 104: 2092–2108.
81. Abdullahi A, Wong TW and Ng SS. Understanding the mechanisms of disease modifying effects of aerobic exercise in people with Alzheimer's disease. *Ageing Res Rev* 2024; 94: 102202.
82. Storch-Hagenlocher B, Reiber H, Wildemann B, et al. Liquordiagnostik. In: Wildemann B, Reiber H and Oschmann P (eds) *Neurologische Labordiagnostik*. Stuttgart: Georg Thieme Verlag KG, 2006, pp.30–73.
83. Zettl UK, Lehmitz R and Mix E. *Klinische Liquordiagnostik*. New York: De Gruyter, 2005.

Supplemental Material

Modulating effects of fitness and physical activity on Alzheimer's disease: Implications from a six-month randomized controlled sports intervention

Supplemental Table 1. Eligibility criteria of the Dementia-MOVE trial.

Inclusion criteria	Exclusion criteria
- Age 50-80 years - Alzheimer's disease or Alzheimer's continuum according to Jack et al. (2018) - MMSE >19 (at least 12 weeks prior to baseline) and/or cognitive abilities for participation in exercise and psychoeducational program - Antidementive and mood-stabilizing medication stable for 30 days - No visual or auditive impairments hindering the participation in testing and intervention - Consent in participation - Interest in regular participation in an intervention program	- Heart attack and/or angina in the last 2 years - Severe systemic disease, with expected degradation during the intervention program - Uncontrolled diabetes mellitus II - Uncontrolled arterial hypertension in the last 6 months - Severe psychiatric disease - Severe orthopedic impairments - Alcohol and/or drug abuse in the last 2 years - Chronic pain or musculoskeletal disease hindering regular participation in sports - Acute fracture or orthopedic disease in the last month - Active cancer in the last 5 years (except basal cell and spinal cell carcinoma of skin) - Exclusion criteria for MRI examination alone: contradiction for 3 T magnetic field (e.g., implantation of ferromagnetic implants)

For an overview of the inclusion and exclusion criteria, see also Haeger et al. Effect of a multicomponent exercise intervention on brain metabolism: A randomized controlled trial on Alzheimer's pathology (Dementia-MOVE). *Alzheimers Dement (N Y)* 2020; 6: e12032. MMSE: Mini-Mental State Examination; MRI: magnetic resonance imaging

Supplemental Table 2. Exemplary exercise plan of the supervised training during the intervention.

Patient's name: XX	<i>Training start date</i>	<i>Medication / secondary diagnoses</i>	HR _{max} (158 /min)	6-MWT (532 m)	VO ₂ max (29.8 ml/min/kg)
Trainers' names: XX					
Exercise	First assessment	1. (date)	2. (date)	3. (date)	[...]
Warm-up (5-10 minutes)					
Ergometer	76 W ^a				
Crosstrainer	100 W				
(Running in place, knee lift, body rotation)					
Coordination training (5-10 minutes)					
Balance plate parcours	10min				
(MFT Fun Disc®, tandem stand, one leg stand, front / side leg raises)					
(Machine) Resistance training (30 minutes)					
Reverse Butterfly	8kg ^b				
Lat pulldown	29kg				
Leg extension	15kg				
Lying leg curl	7kg				
Leg press	58kg				
Hip adduction	28kg				
Hip abduction	14kg				
Rotary torso	-				
Lateral flexion	-				
Abdominal crunch	17 kg				
Back extension	31 kg				
Plank	30 s				
(Sit-ups, Squats, Superman, ...)					
Endurance training (10-15 minutes)					
Ergometer	76 W ^a				
Crosstrainer	100 W				
Hand crank ergometer	-				
(Running in place or outside, cycling)					

Substitute home exercises during the COVID-19 lockdown are shown in brackets. The mean baseline values of the intervention group at baseline are provided for both starting exercise loads and fitness assessment parameters in this explanatory training plan. For resistance training, two exercises per muscle group were selected and alternated throughout the intervention.

^aPeak work load according to Luxton et al. Relationship between field walking tests and incremental cycle ergometry in COPD. *Respirology* 2008; 13: 856–862.

^b40% of one-repetition maximum calculated with the Epley formula

Supplemental Table 3. Spearman's rank correlation analysis of mean daily activity from the Fitbit Charge 2, the physical activity diary and the PAQ50+ questionnaire among all participants included in the analysis.

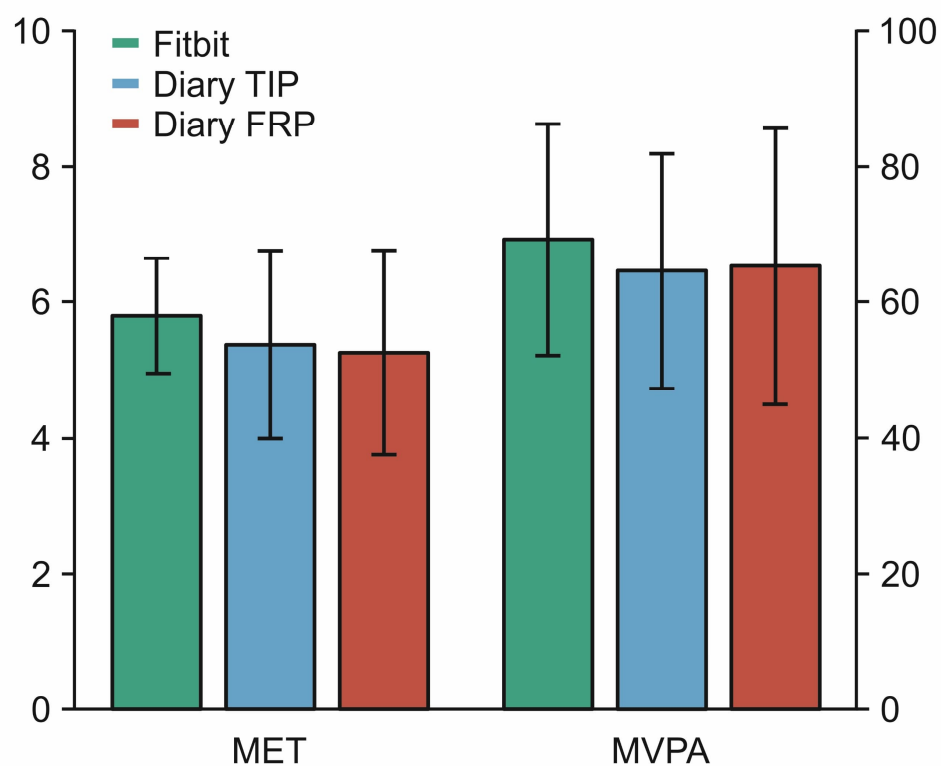
Activity category	<i>M</i>	<i>SD</i>	1	2	3	4	5	6
<i>A</i> Fitbit record period								
1. Fitbit steps	9457	4518						
2. Fitbit MET ^a	5.85	2.69	0.99** [0.98, 0.99]					
3. Fitbit MVPA ^b	67.75	50.14	0.66** [0.45, 0.79]	0.68** [0.45, 0.82]				
4. Diary MET	5.27	4.47	0.50** [0.18, 0.76]	0.52** [0.20, 0.77]	0.38* [0.05, 0.63]			
5. Diary MVPA ^b	65.40	60.19	0.49** [0.15, 0.75]	0.51** [0.20, 0.76]	0.32 [-0.05, 0.60]	0.96** [0.89, 0.98]		
6. PAQ-50+ MET	16.89	8.18	0.46** [0.14, 0.71]	0.47** [0.15, 0.69]	0.32 [0.01, 0.58]	0.48** [0.18, 0.72]	0.41* [0.09, 0.66]	
7. PAQ-50+ MVPA ^b	156.34	82.12	0.48** [0.16, 0.74]	0.48** [0.14, 0.72]	0.51** [0.22, 0.73]	0.59** [0.31, 0.79]	0.54** [0.23, 0.77]	0.84** [0.73, 0.91]
<i>B</i> Total intervention period								
1. Fitbit steps	9504	4216						
2. Fitbit MET ^a	5.84	2.50	0.99** [0.97, 0.99]					
3. Fitbit MVPA ^b	69.43	50.40	0.67** [0.46, 0.80]	0.65** [0.42, 0.79]				
4. Diary MET	5.26	3.95	0.49** [0.19, 0.72]	0.50** [0.21, 0.73]	0.43** [0.13, 0.67]			
5. Diary MVPA ^b	62.92	49.47	0.47** [0.15, 0.71]	0.48* [0.18, 0.72]	0.41* [0.08, 0.65]	0.98** [0.97, 0.99]		
6. PAQ-50+ MET	16.89	8.18	0.46** [0.14, 0.71]	0.45** [0.14, 0.68]	0.33* [0.00, 0.59]	0.39* [0.08, 0.66]	0.36* [0.05, 0.61]	
7. PAQ-50+ MVPA ^b	156.34	82.12	0.48** [0.18, 0.72]	0.46** [0.12, 0.71]	0.51** [0.25, 0.70]	0.50** [0.23, 0.71]	0.48** [0.17, 0.71]	0.84** [0.73, 0.90]

Correlation data of the Fitbit record period (*A*) and the total intervention period (*B*) are presented for comparison. *M* and *SD* are used to represent mean and standard deviation, respectively. Spearman's rank correlation coefficients of the parameters numbered in the first column are indicated. 95% confidence intervals are calculated via BCa bootstrapping with 2000 samples. * $p < 0.05$, ** $p < 0.01$.

The Fitbit record period refers to the mean activity recorded by the Fitbit Charge 2 on the exact days, matched with corresponding diary entries. Missing values: Fitbit ($n = 5$), diary ($n = 5$). For the total intervention period, the mean Fitbit Charge 2 data originates from an average of 11 days of recording between the T2 and T3 assessment points, while mean diary data represents an average of 148 out of 182 days recorded during the intervention period. Missing values: Fitbit ($n = 2$), diary ($n = 2$). Mean values from the German-PAQ-50+ questionnaire were assessed at the T2 and T3 visits and are applied equally for both comparisons.

^a Fitbit MET was estimated from distance output, converted using a moderate standard pace of 4 km/h and a MET value of 3.5 for walking.

^b MVPA: moderate-to-vigorous physical activity with MET > 3 (minutes/day).



Supplemental Figure 1. A bar chart of mean MET and MVPA values, derived from both the Fitbit and the diary, is presented for the total intervention period (TIP) and the Fitbit record period (FRP). No significant differences were detected using the Wilcoxon rank test.

Supplemental Table 4. Results from multiple linear regression analysis of additional fitness parameters (A) 6-MWT distance, (B) postural stability, and (C) handgrip strength

<i>(A) Regression coefficients for predicting change in 6-MWT distance (Δ_{T3-1})</i>					
Variable	<i>B</i>	<i>95% CI</i>	β	<i>t</i>	<i>p</i>
6-MWT distance _{T1}	-0.422	[-0.628, -0.215]	-0.586	-4.134	0.000
Age	-2.335	[-5.023, 0.353]	-0.249	-1.760	0.087
Constant	396.749	[151.611, 641.887]		3.279	0.002
$R^2_{adj} = 0.283$ (N = 40, $p = <0.001$); RMSE 58.099. CI: confidence interval for B					
<i>(B) Regression coefficients for predicting change in postural stability (Δ_{T3-1})</i>					
Variable	<i>B</i>	<i>95% CI</i>	β	<i>t</i>	<i>p</i>
Postural stability _{T1}	-0.354	[-0.587, -0.120]	-0.449	-3.075	0.004
Age	0.017	[0.000, 0.035]	0.289	1.977	0.056
Sex	0.346	[0.110, 0.582]	0.394	2.976	0.005
Constant	-1.326	[-2.595, -0.056]		-2.117	0.041
$R^2_{adj} = 0.373$ (N = 40, $p = <0.001$); RMSE 0.341. CI: confidence interval for B					
<i>(C) Regression coefficients for predicting change in handgrip strength (Δ_{T3-1})</i>					
Variable	<i>B</i>	<i>95% CI</i>	β	<i>t</i>	<i>p</i>
Age	-0.109	[-0.286, 0.067]	-0.197	-1.256	0.217
Sex	-1.695	[-4.103, 0.714]	-0.209	-1.427	0.162
Δ PAQ-50+	0.072	[-0.043, 0.187]	0.184	1.273	0.211
Cov-19 _{adj}	2.712	[0.215, 5.209]	0.334	2.202	0.034
Constant	8.484	[-4.618, 21.587]		1.313	0.197
$R^2_{adj} = 0.268$ (N = 41, $p = 0.004$); RMSE 3.431. CI: confidence interval for B					

Summaries of the best statistical model for all three parameters are presented, indicating the regression coefficient (*B*), its 95% confidence interval (*95% CI*), the standardized regression coefficient (β), the respective *t*-value (*t*), and the significance level (*p*) for each predictor. Additionally, the overall model accuracy is reported, including the adjusted effect size (R^2_{adj}), significance level (*p*), and root mean squared error (*RMSE*). The significance level is defined as $p < 0.05$.

Supplemental Table 5. Detailed summary of the multiple linear regression analysis for predicting changes in disease outcome parameters from CRF increase and physical activity.

(A) Regression coefficients for predicting changes (Δ) in disease outcome parameters via $\Delta VO_2\text{max}$ in the intervention group

Dependent variable (outcome)	Regression parameter	<i>B</i>	95% <i>CI</i>	β	<i>t</i>	<i>p</i>
QoL patient	Baseline	-0.748	[-1.218, -0.278]	-0.596	-3.317	0.003
	Constant	27.510	[9.855, 45.166]		3.250	0.004
QoL family	Baseline	-0.117	[-0.555, 0.321]	-0.131	-0.563	0.581
	Constant	2.515	[-13.120, 18.150]		0.338	0.739
HADS total	$\Delta VO_2\text{max}$	0.825	[-0.317, 1.967]	0.288	1.512	0.147
	Baseline	-0.508	[-0.910, -0.105]	-0.504	-2.641	0.016
	Constant	6.028	[2.537, 9.518]		3.614	0.002
NPI-10	Baseline	0.132	[-0.316, 0.580]	0.154	0.625	0.541
	Constant	-1.520	[-5.941, 2.901]		-0.729	0.477
PSQ-I	Baseline	-0.171	[-0.447, 0.105]	-0.278	-1.294	0.211
	Constant	0.655	[-0.869, 2.179]		0.897	0.380
MoCA	$\Delta VO_2\text{max}$	0.611	[0.035, 1.186]	0.436	2.222	0.039
	Baseline	-0.361	[-0.657, -0.065]	-0.501	-2.555	0.019
	Constant	5.283	[0.092, 10.475]		2.130	0.046
Attention	Baseline	-0.490	[-0.915, -0.065]	-0.474	-2.406	0.026
	Constant	-0.133	[-0.456, 0.189]		-0.863	0.398
Verbal memory	Baseline	-0.829	[-1.454, -0.205]	-0.538	-2.780	0.012
	Constant	0.084	[-0.204, 0.372]		0.611	0.549
Executive functions	$\Delta VO_2\text{max}$	0.089	[0.030, 0.149]	0.515	3.130	0.006
	Baseline	-0.348	[-0.549, -0.147]	-0.597	-3.630	0.002
	Constant	-0.110	[-0.234, 0.014]		-1.851	0.080
Volume HPC	$\Delta VO_2\text{max}$	0.001	[0.000, 0.002]	0.444	2.161	0.044
	Constant	-0.005	[-0.007, -0.003]		-5.776	<0.001
Volume AMG	$\Delta VO_2\text{max}$	<0.001	[0.000, 0.001]	0.486	2.423	0.026
	Constant	-0.001	[-0.002, -0.001]		-3.312	0.004
Volume M-ATL	$\Delta VO_2\text{max}$	0.003	[0.001, 0.005]	0.559	2.940	0.008
	Constant	-0.005	[-0.009, -0.001]		-2.788	0.012
Volume L-ATL	$\Delta VO_2\text{max}$	0.002	[0.000, 0.004]	0.398	1.892	0.074
	Constant	-0.005	[-0.009, -0.001]		-2.498	0.022
Volume PHC	$\Delta VO_2\text{max}$	0.002	[0.000, 0.003]	0.539	2.788	0.012
	Constant	-0.002	[-0.005, 0.000]		-1.949	0.066
Volume STG	$\Delta VO_2\text{max}$	0.003	[0.000, 0.005]	0.441	2.143	0.045
	Constant	-0.010	[-0.016, -0.005]		-4.146	0.001
Volume MTG / ITG	$\Delta VO_2\text{max}$	0.002	[-0.004, 0.008]	0.170	0.753	0.461
	Constant	-0.008	[-0.020, 0.003]		-1.536	0.141
Volume FFG	$\Delta VO_2\text{max}$	0.001	[0.000, 0.002]	0.356	1.662	0.113
	Constant	-0.004	[-0.007, -0.002]		-3.561	0.002
CT HPC	$\Delta VO_2\text{max}$	0.004	[-0.040, 0.048]	0.041	0.179	0.859
	Constant	-0.070	[-0.160, 0.020]		-1.630	0.120
CT AMG	$\Delta VO_2\text{max}$	-0.029	[-0.090, 0.032]	-0.220	-0.984	0.338
	Constant	-0.114	[-0.238, 0.010]		-1.920	0.070
CT	$\Delta VO_2\text{max}$	-0.016	[-0.062, 0.031]	-0.162	-0.715	0.483

M-ATL	Constant	< -0.001	[-0.095, 0.94]		-0.006	0.995
CT	$\Delta VO_2\text{max}$	-0.036	[-0.084, 0.012]	-0.336	-1.555	0.136
L-ATL	Constant	-0.023	[-0.121, 0.075]		-0.489	0.630
CT	$\Delta VO_2\text{max}$	-0.005	[-0.036, 0.025]	-0.084	-0.368	0.717
PHC	Constant	-0.085	[-0.147, -0.022]		-2.838	0.011
CT	$\Delta VO_2\text{max}$	0.001	[-0.013, 0.015]	0.035	0.152	0.881
STG	Constant	-0.024	[-0.053, 0.006]		-1.686	0.108
CT	$\Delta VO_2\text{max}$	0.011	[-0.008, 0.030]	0.263	1.186	0.250
MTG / ITG	Constant	-0.047	[-0.085, -0.008]		-2.548	0.020
CT	$\Delta VO_2\text{max}$	0.005	[-0.021, 0.032]	0.095	0.416	0.682
FFG	Constant	-0.058	[-0.111, -0.004]		-2.254	0.036
Volume	$\Delta VO_2\text{max}$	-0.092	[-0.209, 0.026]	-0.352	-1.637	0.118
Gray matter (total)	Constant	-0.375	[-0.613, -0.136]		-3.290	0.004
CT (total)	$\Delta VO_2\text{max}$	-0.012	[-0.032, 0.009]	-0.261	-1.177	0.254
	Constant	-0.061	[-0.104, -0.019]		-3.040	0.007
Volume	$\Delta VO_2\text{max}$	0.0145	[-0.055, 0.344]	0.329	1.518	0.145
white matter (total)	Constant	-0.030	[-0.435, 0.376]		-0.153	0.880
Volume	$\Delta VO_2\text{max}$	-0.013	[-0.050, 0.024]	-0.163	-0.720	0.480
WML (total)	Constant	0.082	[0.006, 0.158]		2.273	0.035

(B) Regression coefficients for predicting changes (Δ) in disease outcome parameters via $\Delta VO_2\text{max}$ in the control group

Dependent Variable (outcome)	Regression parameter	B	95% CI	β	t	p
QoL patient	Baseline	-0.629	[-1.019, -0.239]	-0.650	-3.419	0.004
	Constant	21.307	[6.779, 35.835]		3.109	0.007
QoL family	$\Delta VO_2\text{max}$	0.576	[-0.379, 1.530]	0.269	1.286	0.218
	Baseline	-0.605	[-1.147, -0.063]	-0.497	-2.377	0.031
	Constant	20.280	[0.961, 39.600]		2.238	0.041
HADS total	$\Delta VO_2\text{max}$	0.229	[-1.422, 1.880]	0.071	0.293	0.773
	Constant	1.842	[-1.880, 5.565]		1.044	0.311
NPI-10	$\Delta VO_2\text{max}$	0.934	[-1.963, 3.831]	0.182	0.692	0.501
	Constant	-1.231	[-7.282, 4.820]		-0.436	0.669
PSQ-I	Baseline	-0.709	[-0.987, -0.432]	-0.795	-5.398	<0.001
	Constant	2.274	[0.419, 4.128]		2.586	0.019
MoCA	$\Delta VO_2\text{max}$	-0.381	[-0.944, 0.182]	-0.327	-1.429	0.171
	Constant	0.53	[-1.217, 1.322]		0.087	0.931
Attention	Baseline	-0.172	[-0.623, 0.279]	-0.191	-0.804	0.433
	Constant	-0.108	[-0.404, 0.189]		-0.766	0.454
Verbal memory	Baseline	-0.854	[-1.404, -0.303]	-0.622	-3.273	0.004
	Constant	0.102	[-0.190, 0.394]		0.738	0.471
Executive functions	Baseline	-0.330	[-0.631, -0.029]	-0.490	-2.316	0.033
	Constant	0.053	[-0.138, 0.243]		0.583	0.568
Volume HPC	$\Delta VO_2\text{max}$	< -0.001	[-0.001, 0.001]	-0.022	-0.082	0.936
	Constant	-0.001	[-0.004, 0.002]		-0.555	0.588
Volume AMG	$\Delta VO_2\text{max}$	< -0.001	[-0.001, 0.000]	-0.236	-0.909	0.379
	Constant	-0.001	[-0.001, 0.000]		-1.453	0.168
Volume	$\Delta VO_2\text{max}$	-0.002	[-0.005, 0.001]	-0.363	-1.456	0.168

M-ATL	Constant	-0.002	[-0.008, 0.003]		-0.883	0.392
Volume	$\Delta VO_2\text{max}$	<0.001	[-0.002, 0.002]	0.073	0.275	0.787
L-ATL	Constant	-.002	[-0.006, 0.002]		-0.956	0.355
Volume	$\Delta VO_2\text{max}$	<0.001	[-0.001, 0.002]	0.050	0.188	0.854
PHC	Constant	< -0.001	[-0.003, 0.003]		-0.009	0.993
Volume	$\Delta VO_2\text{max}$	< -0.001	[-0.003, 0.002]	-0.092	-0.345	0.736
STG	Constant	-0.001	[-0.007, 0.005]		-0.448	0.661
Volume	$\Delta VO_2\text{max}$	0.002	[-0.003, 0.007]	0.192	0.732	0.476
MTG / ITG	Constant	0.002	[-0.008, 0.012]		0.458	0.654
Volume	$\Delta VO_2\text{max}$	<0.001	[-0.001, 0.001]	0.189	0.720	0.483
FFG	Constant	<0.001	[-0.002, 0.002]		0.023	0.982
CT	$\Delta VO_2\text{max}$	-0.016	[-0.046, 0.015]	-0.281	-1.094	0.292
HPC	Constant	0.045	[-0.019, 0.109]		1.523	0.150
CT	$\Delta VO_2\text{max}$	-0.018	[-0.095, 0.058]	-0.136	-0.512	0.617
AMG	Constant	-0.020	[-0.182, 0.141]		-0.268	0.793
CT	$\Delta VO_2\text{max}$	0.018	[-0.024, 0.061]	0.239	0.920	0.373
M-ATL	Constant	-0.090	[-0.180, -0.001]		-2.160	0.049
CT	$\Delta VO_2\text{max}$	0.006	[-0.028, 0.039]	0.096	0.359	0.725
L-ATL	Constant	-0.088	[-0.158, -0.019]		-2.732	0.016
CT	$\Delta VO_2\text{max}$	-0.013	[-0.047, 0.021]	-0.219	-0.842	0.414
PHC	Constant	-0.008	[-0.079, 0.063]		-0.240	0.814
CT	$\Delta VO_2\text{max}$	0.010	[-0.009, 0.030]	0.288	1.125	0.279
STG	Constant	-0.003	[-0.044, 0.038]		-0.153	0.881
CT	$\Delta VO_2\text{max}$	0.015	[-0.007, 0.037]	0.363	1.460	0.166
MTG / ITG	Constant	-0.066	[-0.112, -0.020]		-3.058	0.009
CT	$\Delta VO_2\text{max}$	-0.009	[-0.059, 0.040]	-0.107	-0.402	0.694
FFG	Constant	-0.073	[-0.177, 0.032]		-1.495	0.157
Volume	$\Delta VO_2\text{max}$	0.103	[-0.068, 0.274]	0.328	1.298	0.215
Gray matter (total)	Constant	-0.398	[-0.757, -0.038]		-2.374	0.032
CT (total)	$\Delta VO_2\text{max}$	0.001	[-0.014, 0.017]	0.043	0.161	0.875
	Constant	-0.040	[-0.073, -0.008]		-2.650	0.019
Volume	$\Delta VO_2\text{max}$	-0.105	[-0.299, 0.090]	-0.294	-1.152	0.269
white matter (total)	Constant	0.321	[-0.088, 0.730]		1.684	0.114
Volume	$\Delta VO_2\text{max}$	<0.001	[-0.014, 0.015]	0.019	0.069	0.946
WML (total)	Constant	0.017	[-0.014, 0.048]		1.172	0.261

(C) Regression coefficients for predicting changes (Δ) in disease outcome parameters via Fitbit step count in the overall cohort

Dependent Variable (outcome)	Regression parameter	B	95% CI	β	t	p
QoL patient	Baseline	-0.677	[-0.971, -0.384]	-0.604	-4.671	<0.001
	Constant	24.077	[13.093, 35.062]		4.437	<0.001
QoL family	Step count	<0.001	[0.000, 0.001]	0.381	2.482	0.018
	Baseline	-0.463	[-0.778, -0.149]	-0.461	-3.000	0.005
	Constant	11.312	[0.435, 22.190]		2.116	0.042
HADS total	Baseline	-0.263	[-0.587, 0.061]	-0.255	-1.644	0.108
	Constant	4.339	[1.100, 7.578]		2.710	0.010
NPI-10	Step count	<0.001	[-0.001, 0.000]	-0.263	-1.589	0.123
	Baseline	-0.275	[-0.498, -0.052]	-0.418	-2.523	0.017

	Constant	3.528	[-1.692, 8.747]		1.380	0.178
PSQ-I	Baseline	-0.468	[-0.674, -0.262]	-0.593	-4.601	<0.001
	Constant	1.476	[0.223, 2.729]		2.382	0.022
MoCA	Step count	<0.001	[0.000, 0.000]	0.122	0.751	0.458
	Constant	-1.057	[-3.114, 1.000]		-1.041	0.305
Attention	Baseline	-0.361	[-0.647, -0.074]	-0.377	-2.543	0.015
	Constant	-0.094	[-0.298, 0.111]		-0.926	0.360
Verbal memory	Baseline	-0.838	[-1.212, -0.463]	-0.592	-4.530	<0.001
	Constant	0.091	[-0.095, 0.277]		0.993	0.327
Executive functions	Step count	<0.001	[0.000, 0.000]	0.370	2.662	0.012
	Baseline	-0.229	[-0.390, -0.067]		-2.873	0.007
	Constant	-0.334	[-0.586, -0.082]		-2.686	0.011
Volume HPC	Step count	<0.001	[0.000, 0.000]	0.122	0.717	0.478
	Constant	-0.005	[-0.009, 0.000]		-2.110	0.042
Volume AMG	Step count	< -0.001	[0.000, 0.000]	-0.072	-0.421	0.676
	Constant	-0.001	[-0.002, 0.001]		-1.018	0.316
Volume M-ATL	Step count	< -0.001	[0.000, 0.000]	-0.118	-0.695	0.492
	Constant	-0.002	[-0.011, 0.007]		-0.425	0.674
Volume L-ATL	Step count	< -0.001	[0.000, 0.000]	-0.254	-1.531	0.135
	Constant	0.001	[-0.006, 0.008]		0.271	0.788
Volume PHC	Step count	< -0.001	[0.000, 0.000]	-0.206	-1.229	0.228
	Constant	0.002	[-0.004, 0.007]		0.580	0.566
Volume STG	Step count	< -0.001	[0.000, 0.000]	-0.112	-0.659	0.514
	Constant	-0.003	[-0.014, 0.007]		-0.639	0.527
Volume MTG / ITG	Step count	< -0.001	[0.000, 0.000]	-0.214	-1.277	0.210
	Constant	0.007	[-0.012, 0.026]		0.759	0.453
Volume FFG	Step count	< -0.001	[0.000, 0.000]	-0.080	-0.470	0.642
	Constant	-0.001	[-0.006, 0.003]		-0.625	0.536
CT HPC	Step count	< -0.001	[0.000, 0.000]	-0.352	-2.192	0.035
	Constant	0.114	[-0.025, 0.253]		1.666	0.105
CT AMG	Step count	<0.001	[0.000, 0.000]	0.044	0.259	0.797
	Constant	-0.095	[-0.330, 0.141]		-0.817	0.420
CT M-ATL	Step count	<0.001	[0.000, 0.000]	0.202	1.200	0.239
	Constant	-0.124	[-0.285, 0.037]		-1.569	0.126
CT L-ATL	Step count	<0.001	[0.000, 0.000]	0.371	2.330	0.026
	Constant	-0.206	[-0.356, -0.056]		-2.788	0.009
CT PHC	Step count	< -0.001	[0.000, 0.000]	-0.191	-1.132	0.266
	Constant	0.004	[-0.110, 0.119]		0.078	0.938
CT STG	Step count	< -0.001	[0.000, 0.000]	-0.141	-0.829	0.413
	Constant	0.006	[-0.051, 0.064]		0.227	0.822
CT MTG / ITG	Step count	< -0.001	[0.000, 0.000]	-0.028	-0.161	0.873
	Constant	-0.047	[-0.120, 0.027]		-1.290	0.206
CT FFG	Step count	<0.001	[0.000, 0.000]	0.096	0.564	0.576
	Constant	-0.098	[-0.225, 0.029]		-1.565	0.127
Volume Gray matter (total)	Step count	<0.001	[0.000, 0.000]	0.231	1.385	0.175
	Constant	-0.677	[-1.177, -0.177]		-2.752	0.009
CT (total)	Step count	<0.001	[0.000, 0.000]	0.002	0.010	0.992
	Constant	-0.053	[-0.122, 0.016]		-1.562	0.127
Volume white matter (total)	Step count	< -0.001	[0.000, 0.000]	-0.244	-1.467	0.152
	Constant	0.584	[-0.131, 1.298]		1.660	0.106

Volume	Step count	<0.001	[0.000, 0.000]	0.213	1.272	0.212
WML (total)	Constant	-0.011	[-0.122, 0.100]		-0.195	0.846

Summary of multiple linear regression models predicting disease outcome (dependent variable) via $\Delta\text{VO}_2\text{max}$ in A) the intervention group, B) the control group as well as via C) via Fitbit step count in the overall cohort. The disease outcome (dependent variable) represents the change (Δ) in the corresponding parameter calculated by T_3 minus T_1 . The best models were chosen according to their overall model accuracy determined via the adjusted effect size (R^2_{adj}), significance level (P), and root mean squared error ($RMSE$) as indicated in the main article. Baseline indicates the corresponding results of the outcome variable at timepoint T_1 . Indicated is further the regression coefficient (B), its 95% confidence interval (95% CI), the standardized regression coefficient (β), the respective t-value (t), and the significance level (p) for each predictor. Significance level is defined as $p < 0.05$.

QoL: quality of life; HADS: Hospital Anxiety and Depression Scale; NPI-10: Neuropsychiatric Inventory; PSQ-I: Pittsburgh Sleep Quality Index; MoCA: Montreal Cognitive Assessment; HPC: hippocampus; AMG: amygdala; M-ATL: medial anterior temporal lobe; L-ATL: lateral anterior temporal lobe; PHC: parahippocampal and ambient gyri; STG: superior temporal gyrus; MTG/ITG: middle and inferior temporal gyri; FFG: fusiform gyrus; CT: cortical thickness; WML: white matter lesion.



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Physical activity monitoring in Alzheimer's disease during sport interventions: a multi-methodological perspective

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Introduction: Assessment methods for physical activity and fitness are of upmost importance due to the possible beneficial effect of physical conditioning on neurodegenerative diseases. The implementation of these methods can be challenging when examining elderly or cognitively impaired participants. In the presented study, we compared three different assessment methods for physical activity from the Dementia-MOVE trial, a 6-months intervention study on physical activity in Alzheimer's disease. The aim was to determine the comparability of physical activity assessments in elderly participants with cognitive impairment due to Alzheimer's disease.

Material or methods: 38 participants (mean age 70 ± 7 years) with early-stage Alzheimer's disease (mean MoCA 18.84 ± 4.87) were assessed with (1) fitness trackers for an average of 12 (± 6) days, (2) a written diary on daily activities and (3) a questionnaire on physical activity at three intervention timepoints. For comparison purposes, we present a transformation and harmonization method of the physical assessment output parameters: Metabolic equivalent of task (MET) scores, activity intensity minutes, calorie expenditure and moderate-to-vigorous physical activity (MVPA) scores were derived from all three modalities. The resulting parameters were compared for absolute differences, correlation, and their influence by possible mediating factors such as cognitive state and markers from cerebrospinal fluid.

Results: Participants showed high acceptance and compliance to all three assessment methods. MET scores and MVPA from fitness trackers and diaries showed high overlap, whilst results from the questionnaire suggest that participants tended to overestimate their physical activity in the long-term retrospective assessment. All activity parameters were independent of the tested Alzheimer's disease parameters, showing that not only fitness trackers, but also diaries can be successfully applied for physical activity assessment in a sample affected by early-stage Alzheimer's disease.

Discussion: Our results show that fitness trackers and physical activity diaries have the highest robustness, leading to a highly comparable estimation of physical activity in people with Alzheimer's disease. As assessed parameters, it is recommendable to focus on MET, MVPA and on accelerometric sensor data such as step count, and less on activity calories and different activity intensities which are dependent on different variables and point to a lower reliability.

KEYWORDS

physical activity intervention, exercise, fitness, Alzheimer's disease, dementia, wearables, mobile health, fitness tracker

Introduction

The rising incidence of dementia, and especially Alzheimer's disease (AD) as the most common form, represents a major public health challenge, imposing not only on the people affected, but also on our entire society and health system (1). Next to pharmacological therapies, intervention studies investigating the effects of modifiable risk factors in delaying or preventing dementia, have suggested that improved physical activity and cardiorespiratory fitness could slow down cognitive decline and positively influence brain pathology in neurodegeneration (2–5), either as a stand-alone or as add-on on primary and secondary therapies (6–9). The individual contribution to brain pathology and neurodegeneration on the general physical activity level, on the one hand, and cardiorespiratory fitness, on the other hand, assessed, e.g., by the maximal oxygen uptake ($\text{VO}_{2\text{max}}$), is still not clear and rarely differentiated in intervention studies in AD (2).

In the context of this type of intervention studies, tracking physical activity and cardiorespiratory fitness is a major challenge, especially in elderly and cognitively impaired people. Such challenges are related to issues with patient's acceptability and compliance, increased susceptibility to biases (e.g., social desirability bias), but also lack of reference values that adjust for confounders, such as age and motor disability (10, 11). Beyond classical approaches for monitoring physical activity that use self-report, such as diaries and standardized questionnaires, focus is now set on a new field using wearable and affordable fitness trackers and mobile health devices (12, 13). Besides recording physical activity data, this type of devices also offer additional options to track sleep parameters enabling and objectifying the investigation of neuropsychiatric health and impairment of the autonomic nervous system in AD and therefore link to behavioral symptoms in AD pathology (14). Still, intervention studies of physical activity and cardiorespiratory fitness in AD that apply these types of devices are scarce.

The Dementia-MOVE study is a six-months randomized-controlled intervention study to investigate the effect of physical activity and cardiorespiratory fitness on AD progression. Three different methods were used for the assessment of physical activity and individual cardiorespiratory fitness levels: (1) a wearable fitness tracker for the recording of physical activity and sleep, (2) a written diary, in which participants recorded their daily physical activities and sleep duration and (3) a standardized questionnaire on physical activity in the previous month. In the present study, we compare these three different fitness / activity tracking methods in terms of feasibility and reliability in a group of elderly cognitively impaired people in the context of an intervention study. Our aim is to clarify how accurate and feasible the assessment of physical activity and fitness in people with AD is, and in such a way to contribute to increased quality standards for upcoming intervention studies.

Methods

The Dementia-MOVE multicomponent intervention program in Alzheimer's disease

The Dementia-MOVE study (Multi-Objective Validation of Exercise in Dementia) is a six-months randomized-controlled clinical trial with two arms, including a group participating in an exercise intervention program compared to a group participating in a pure psychoeducational program (control group). A total of 46 people diagnosed with prodromal or mild AD according to NIA-AA Research Framework criteria (15) were included in the trial. People aged between 50 and 80 years that were cognitively and physically able to participate in the whole study program were considered eligible. After baseline assessments (timepoint T1), participants were randomized into either the exercise intervention group ($n=26$) or a control group ($n=20$), using the WINPEPI software (16). Randomization was performed blinded for clinical information, balancing for age and fitness level ($\text{VO}_{2\text{max}}$ or 6-min walk distance). Further outcome assessments were collected after three (timepoint T2) and 6 months (timepoint T3). From the outcome assessments, in this study we focused on fitness assessment using the 6-min walk test (6-MWT) (17) and estimated $\text{VO}_{2\text{max}}$ determined by an ergometer protocol (18), as well as global cognitive performance using the Montreal Cognitive Assessment (MoCA) screening test (19), the Clinical Dementia Rating (CDR) (20) and neuropsychiatric symptoms, namely the Hospital Anxiety and Depression Scale (HADS) (21). The exercise intervention included both a weekly training program guided by physiotherapists, as well as a home-based training program. For the home-based training, participants were instructed to undergo physical training at home for at least 30 min a week, with moderate exertion according to the Borg rating of perceived exertion (RPE) scale adapted to people with dementia, and received instructions for stretching and toning exercises, which they should also perform twice a week for 15 min (22, 23). The control group was instructed to perform their physical activity as usual and received monthly psychoeducational sessions, in which the intervention group also participated. During the lockdown period due to the SARS-CoV2 pandemic, which affected a subgroup of participants, all intervention was changed to a home-based program and narrowly monitored by regular phone calls and reminders.

The study and all protocol changes were approved by the local ethics committee (EK 306/18) and performed according to the latest Declaration of Helsinki. All participants gave written informed consent to study participation and protocol changes. The trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03939286) (NCT03939286). The targeted sample size was initially set to 50 people, based on power analyses and previous intervention studies with physical activity. The detailed study protocol is described in Haeger et al. (24).

For the current analyses on activity monitoring, we included participants with a complete set of data. This implied that the recorded days of the fitness tracker had matching diary entries and excluded participants who dropped-out during the course of the study. Thus, the data presented here arises from a final sample of 38 participants, regardless of group randomization assignment.

Assessment of physical activity

Assessment of physical activity via wearable fitness trackers

We used a commercially available wrist-worn fitness tracker (Fitbit Charge 2®) to determine activity levels (step counts, activity intensity and frequency). We created an anonymized Fitbit account for each participant, including individual relevant information (age, gender, weight and height). Participants used the devices for an average of 14 days around the T2 timepoint. They were instructed to wear the tracker also at night and to take it off only for showering and recharging in case of battery depletion. Since elderly and cognitively impaired study participants not always use smartphone devices and are therefore not necessarily able to regularly synchronize their fitness trackers, the devices were distributed on a normally weekly to biweekly basis. Intermittently, the devices were collected, synchronized by the study team and then handed out again. Following this strategy, there was a low efficiency due to overwriting of the device's internal memory when time intervals between account synchronizations were too long. To generate as many physical activity information as possible, we then moved to regular synchronization at home at least every 3 days by instructing the participants and their caregivers. In case no smartphone was available, the trackers were synchronized via the first described method, so the possession of a smartphone was no eligibility criterion for study participation. Data generated by the device included the walking distance, step count, floors count, active minutes (divided in three rates from light to moderate and vigorous intensity), as well as activity calorie and total calorie consumption.

Assessment of physical activity via a written diary

As a second method, a paper-based physical activity written diary was distributed to participants, together with an information and instructional letter. By telephone, participants and their caregivers were verbally instructed about the correct usage of the diary. The diary took the physical form of a folder with removable sheets, with each page offering a weekly overview, with fields to enter the type and duration of daily activities, physical complaints during exercise, subjective physical exertion estimated via the Borg RPE scale (22), hours of sleep, medication taken, weight (measured once per week), and additional comments, such as current health complaints. All participants, independent of group randomization assignment, completed the diary. For the intervention group, rows to document each of the weekly training sessions were also available. An exemplary diary page translated into English can be found in [Supplementary Table S1](#). To minimize the risk of missing data due to loss of single diary pages, completed pages were collected as often as possible, for example during the monthly psychoeducational lectures, study visits, as well as the supervised trainings for the intervention

group. The collected pages were then checked by the study team and participants and their relatives were again instructed, in the case of incompleteness or inaccuracy to avoid recall issues. As the people included in the study had a CDR score of 0.5 to 1 on average indicating a relatively preserved autonomy, keeping a diary was possible. The presence of a caregiver was therefore not obligatory, however, only one participant in our study sample did not have relatives (either a partner or children) for support at home. The diary had to be filled out during the whole 26 weeks of study participation. For nine participants, the T3 visit had to be postponed for 9 weeks due to the SARS-CoV-2 lockdown. The intervention protocol was kept the same during this period and only changed to a home-based program with similar exercises. The participants were instructed to continue keeping the diary for this additional time to keep track of their physical activity, until the final outcome assessments were feasible.

Assessment of physical activity via the PAQ50+ questionnaire

The PAQ50+ is a structured questionnaire for recording physical activity, especially designed for people over the age of 50 years (25). The PAQ50+ is based on the Yale Physical Activity Surveys and the Physical Activity Scale for the Elderly and measures how much time a person has spent on various activities over the past 4 weeks, in terms of hours per week (26, 27). It has been shown to be reliable in estimating both total physical activity and energy expenditure (28). It offers space to enter the time spent on 37 predefined activities from various categories such as housework, gardening, leisure time, sport, and occupation as well as further individual activities. Each activity determines a certain metabolic equivalent of task (MET)-score, which leads in combination with the total duration of the activity and the weight of the person to the estimation of the energy expenditure. The total score of the PAQ50+ is calculated by the sum of all activities in kilocalories per week. The PAQ50+ was administered to participants at all timepoints of study participation (baseline T1, T2, T3).

Physical activity data processing and transformation

The primary aim of data transformation was to standardize the output of the assessment tools to enable a reliable comparison between the different methods. Data of all three methods were processed based on MET scores. One MET is equal to the energy cost of sitting quietly and represents an estimation of the degree of energy expenditure of individual activities put in relation (29). Using this method, activities were converted according to their intensity to MET-hours per day applying the following equation based on Ainsworth et al. (30):

$$\text{Daily MET} = \sum_{n=1}^A \frac{t_n \times \text{MET}_n}{60}, \quad (1)$$

with A being the number of distinct daily activities performed, t_n the time in minutes spent on activity n , weighted by its individual MET (MET_n).

In general, all activities with a MET >3 were defined as physical activity, based on the recommendations for physical activity according to the American College of Sports Medicine (31), and specified in

previous literature (30, 32, 33), as well as on the Fitbit website.¹ The estimation of active minutes from the Fitbit device is based on MET scores to estimate the exercise intensity. The Fitbit therefore demands an activity >3 MET to be continuously performed for at least 10 min to be recorded (34). An additional daily MET score was calculated first converting the Fitbit walking distance (in kilometers) to a time unit (in hours) by dividing it by a standard pace of 4 km/h and then multiplying it with a MET of 3.5 for walking (30). For the subsequent analyses, the moderate and vigorous intensities of physical activity were used and their sum cumulated in a moderate-to-vigorous physical activity (MVPA) score, as these cover the generally recommended training intensity for physical activity (32). We further applied the activity calories given by the fitness tracker in the analyses.

To enable a conversion to MET scores from the written diary, all entries were initially digitized and standardized indicating the activity and the time spent in minutes to meet the calculation requirements for eq. (1) above. MET scores of entries originally specified in distance units were computed as follows:

$$\text{Daily MET} = \sum_{n=1}^A \left(\frac{d_n}{p_n} \right) \times \text{MET}_n, \quad (2)$$

with A being the number of distinct daily activities performed, d_n the distance covered during the activity n in kilometers, divided by a predefined low-to-moderate intense standard pace p_n in kilometers per hour as to be expected in the elderly, and multiplied by its individual MET_n (30).

Entries with no time or distance information given were set to 30 min in general and 15 min for stretching and toning tasks, as these were the given instructions on time-duration for these additional home-based activities in the intervention group (24). A daily MET score was calculated for each day as the sum of all activities performed following the equations above. However, low-effort activities with a $\text{MET} < 2$ were priorly filtered out for interindividual homogenization of the entries (30). Analogously to the Fitbit output, active minutes were computed based on previously defined MET thresholds indicating moderate exercise with a MET of 3–5.9 and vigorous activity with a $\text{MET} \geq 6$ (30, 32, 33). Furthermore, activity calories were calculated by multiplying the daily MET score with the participant's weight in kilograms as instructed in the PAQ50+ questionnaire.

The processing of the PAQ50+ data was carried out analogously to the physical activity diary. As mentioned before, MET scores for the 37 activities in the PAQ50+ are already included in the questionnaire. MET scores of individual entries were complemented using the same publication as for the physical activity diary (30). To enable comparison between methods, an average daily score was calculated by dividing the original weekly PAQ50+ score by 7.

The data transformation was carried out automatically using a program written in the Python programming language version 3.9² implementing the processing rules listed above. Out of all variables examined, MET and MVPA were prioritized being the presumably

most informative parameters to assess the basic physical activity level. The subdivided activity minutes scores as well as activity calories were additionally analyzed to supply further information on each method's accuracy and potential differences in the data transforming process.

All three methods were compared based on the total data acquired during the intervention period. A mean value of the T2 and T3 scores only was calculated for the PAQ50+ as the T1 assessment referred to the time-period before the intervention start. Fitbit and physical activity diary were additionally compared focusing only on the recorded days and their corresponding diary entries.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 26 software.³ An explorative data analysis revealed a non-normally distributed data structure of activity monitoring data, therefore nonparametric tests were used for comparison. Absolute parameters of all three methods as mentioned above were first compared for differences using mean, standard deviation, median, median absolute deviation, and the Wilcoxon-Test. Correlation analysis was performed using Spearman's rank correlation including 95% confidence intervals computed via BCa-Bootstrapping with 2,000 samples. Bland-Altman-Plots were built to further visualize the fluctuation range of diary and PAQ50+ MET data compared to the objective fitness tracker assessments (35, 36). To control for possible influencing factors, additional partial correlations were performed controlling for cerebrospinal fluid (CSF) parameters such as amyloid- β 1–42, amyloid- β 42/40-ratio, tau, and phospho-tau as markers of neurodegeneration in AD, the MoCA score, the HADS, and years of education. Zero-order correlations of each analysis were also examined for significant associations between the fitness parameters and the correcting variable, to further analyze a noticeable stronger deviation of the partial correlation coefficients from the uncorrected analysis. Note that the sample size for partial correlation analyses correcting for CSF markers is reduced to $n=35$, and $n=34$ for amyloid- β 42/40-ratio, respectively, since three participants did not have CSF diagnostics. Each analysis was Bonferroni-Holm corrected for multiple comparisons, with significant results reported at a corrected p -value < 0.05 .

Results

Basic characteristics of the study sample

Mean age of the study sample was $70 (\pm 7)$ years, including 13 women and 25 men. In the baseline fitness assessment, the participants reached an average VO_2max of $29.59 (\pm 5.74)$ ml/kg/min and covered a mean distance of $538 (\pm 97)$ meters in the 6-Minute-Walk-Test. The average body mass index (BMI) was $24.32 (\pm 4.28)$ kg/m². The average brief cognitive screening MoCA score was $18.84 (\pm 4.87)$, the CDR mean score was $0.75 (\pm 0.38)$, marking a mild disease stage (20). A description of the included sample is given in Table 1.

1 https://help.fitbit.com/articles/en_US/Help_article/1379.htm

2 <https://www.python.org>

3 <https://www.ibm.com/products/spss-statistics>

TABLE 1 Basic characteristics of the analyzed sample ($n = 38$).

Sample characteristics	N	M	SD	Min	Max
Age (years)	38	69.63	7.32	50	80
Sex (m/f)	38	25/13			
Education (years)	38	13.34	3.6	5	21
CDR	38	0.75	0.38	0	2
CSF Amyloid- β 1–42 (pg/ml) ^a	35	414.97	170.63	135	841
CSF Amyloid- β 42/40-ratio ^a	34	0.42	0.2	0.18	1.3
CSF Tau (pg/ml) ^a	35	611.69	323.32	135	1,285
CSF Phospho-Tau (pg/ml) ^a	35	85.20	35.39	24	191
MoCA	38	18.84	4.87	10	28
HADS	38	7.92	6.54	0	25
VO ₂ max (ml/min/kg)	38	29.59	5.74	16.55	45.93
6-MWT (m)	38	537.74	97.38	331.6	781
BMI (kg/m ²)	38	24.32	4.28	18.71	41.77

^aLab-specific AD-relevant cut-off values for cerebrospinal fluid parameters are as follows: amyloid- β 1–42 < 450 pg/ml, amyloid- β 42/40-ratio < 0.5, tau > 450 pg/ml, phospho-tau > 61 pg/ml, analysis being performed in the Neurochemical Laboratory at the University of Göttingen (37, 38).

Overview of the characteristics of the presented study sample: Sample size N , mean values M , standard deviations SD and range (Min, Max values) are presented. CDR, Clinical Dementia Rating; MoCA, Montreal Cognitive Assessment; HADS, Hospital Anxiety and Depression Scale; VO₂max, maximal oxygen uptake (in ml/kg/min); 6-MWT, 6-Minute Walk Test (in meters); BMI, body mass index (in kg/m²); CSF, cerebrospinal fluid.

Adherence to physical activity acquisitions

The Fitbit tracker was distributed to the participants for approximately 14 days, providing an average of $12 (\pm 6)$ completely registered days. The compliance for wearing the fitness trackers was 100%. For the written diary, calculation of the compliance refers to 26 weeks of intervention and, thus, 182 editable daily columns, which were accepted as completed, if at least one row per day was filled out by the participant. According to these considerations, mean diary compliance was altogether high with $87\% (\pm 20\%)$. The PAQ50+ questionnaire was filled out by 100% of the 38 participants included in this analysis at all three acquisition timepoints.

Comparison of physical activity assessment methods

First, we compared mean data from matching fitness tracker recording days and corresponding diary entries (see Table 2). Mean MET (5.73 ± 2.67 vs. 5.12 ± 4.41) as well as MVPA values (66.31 ± 49.33 vs. 63.47 ± 59.16) were not statistically different (for MET: $z = -1.47$, $p = 0.71$; for MVPA: $z = -0.76$, $p = 0.45$), revealing a high association between fitness tracking and subjective estimation of activity noted by the participants in the diaries. However, when differentiating between minutes spent on moderate and vigorous activity, data from the tracker and the diary were discrepant (moderate intensity, $z = -1.25$, $p = 0.63$; vigorous intensity, $z = -4.07$, $p < 0.001$), and suggesting differences in the subdivision algorithm between both methods. When comparing the registered activity from the fitness trackers with the activity noted in the diaries during the whole intervention period,

MET and MVPA were similar, pointing to a high rate of transferability of the activity results of the registered fitness trackers period to the whole period of the intervention (MET, $z = -1.39$, $p = 0.66$; MVPA, $z = -0.78$, $p = 0.88$).

Furthermore, we compared results of the PAQ50+ questionnaire with the fitness trackers and the diaries. Therefore, activity derived from the PAQ50+ at timepoints T2 and T3 was averaged, since only activity during the intervention period was of interest for this analysis. We noticed that even though the questionnaire was similarly subjective compared to the diary assessment, activity reported in the PAQ50+ was higher (MET, 16.42 ± 8.53 ; MVPA 154.21 ± 83) compared to the fitness tracker (MET, $z = -5.33$, $p < 0.001$; MVPA, $z = -4.92$, $p < 0.001$) and the diary (MET, $z = -5.2$, $p < 0.001$; MVPA, $z = -5.16$, $p < 0.001$). A difference in all three methods was also reflected in the activity calorie consumption (Fitbit, $1,116 \pm 447$; diary, 375 ± 317 ; PAQ50+, $1,135 \pm 656$).

In the correlation analysis, MET values of all three methods were moderately correlated (Fitbit vs. diary, $\rho = 0.54$, $p = 0.01$; Fitbit vs. PAQ50+, $\rho = 0.46$, $p = 0.03$; diary vs. PAQ50+, $\rho = 0.44$, $p = 0.04$) (Figure 1 and Supplementary Table S2). This effect was also reflected by the MVPA scores (Fitbit vs. diary, $\rho = 0.48$, $p = 0.03$; Fitbit vs. PAQ50+, $\rho = 0.55$, $p = 0.01$; diary vs. PAQ50+, $\rho = 0.59$, $p = 0.01$), pointing to a proportional association of these main parameters between all three methods. In line with the discrepancies in the descriptive analysis, a lower level of agreement was observed between diary and Fitbit subdivided moderate and vigorous activity scores (moderate intensity, $\rho = 0.31$, $p = 0.18$; vigorous intensity, $\rho = 0.34$, $p = 0.18$). Interestingly, activity calories were also highly correlated despite presenting strong differences in the comparison of absolute data (see again Supplementary Table S2).

We furthermore illustrated the data in Bland–Altman-Plots to visualize the agreement between the subjective estimated MET deriving from the diary or questionnaire and the fitness tracker data based on each method's total mean values (see Figure 2): In the plot for diary and Fitbit MET, an average difference between the two instruments $MET_{\text{Fitbit-Diary}}$ close to zero (0.45 ± 2.90) suggested a good overlap among the absolute values. The majority of data points were randomly located around the mean line and within the tolerance range pointing to a measurement with very low bias. Only two data points were detected as minimal outliers, however one overestimating and the other one underestimating physical activity in the diary compared to the Fitbit, so that a random error can be assumed. The plot considering PAQ50+ and Fitbit MET however confirmed the previously raised assumption that physical activity in the questionnaire was overestimated. While the mean difference $MET_{\text{Fitbit-PAQ50+}}$ already showed a negative deviation (-10.73 ± 7.67), almost all data points in the scatterplot were also located in the negative range leading to a structured error in the PAQ50+ data. When looking at the point cloud it is also striking that there seems to be a proportional bias with an increasing overestimation of physical activity at higher mean values. Again, one subject was detected being outside the 95% limits of agreement.

Influence of confounding factors

As a further step, we aimed to identify confounding factors, which could have an impact on fitness and activity assessments. We therefore

TABLE 2 Descriptive statistics of the three applied physical activity assessment methods.

Methods	Steps	MET score	Moderate activity (min)	Vigorous activity (min)	MVPA (min)	Activity calories (kcal)
Fitbit	9,262 (4478)	5.7 (2.7)	32.2 (28.4)	34.1 (27.6)	66.3 (49.3)	1,114 (447)
	8,222 (2373)	4.9 (1.5)	22.2 (10.5)	30.5 (15.3)	51.2 (27)	1,042 (332)
Diary		5.1 (4.4)	51.4 (60.4)	12.1 (14.5)	63.5 (59.2)	365 (349)
		3.7 (1.9)	29 (19.2)	6.7 (5.4)	41.2 (20.7)	286 (143)
PAQ50+		16.4 (8.5)	126.7 (74.6)	27.5 (30.5)	154.2 (83)	1,135 (656)
		16.7 (6.2)	115.7 (41.8)	18.2 (10.7)	139.3 (50.4)	1,042 (362)

Daily mean values and standard deviations of Fitbit, diary and PAQ50+ are presented, as well as median values and median absolute deviations in italics. Indicated values of Fitbit and diary refer to Fitbit recording days with matching diary entries only. For the PAQ50+ mean values of the T2 and T3 acquisitions were used. MET, metabolic equivalent of task; MVPA, moderate-to-vigorous physical activity (in minutes).

performed partial correlation analyses comparing the objective Fitbit MET and MVPA data to our diary and PAQ50+ data, controlling for conceivable factors such as cerebrospinal amyloid- β 1–42, amyloid- β 42/40-ratio, tau, phospho-tau, MoCA as well as HADS score and years of education. Corresponding zero-order correlations to check for associations between the tested and the correcting variables were also included to rule out non-conclusive deviations of the corrected analysis compared to the uncorrected correlation. Summarizing these results, MET and MVPA data of both the diary and the PAQ50+ appeared robust against the correction (see Table 3). The majority of corrected correlation coefficients presented a percentage difference lower than 0.1 compared to the uncorrected analysis. Only the partial correlation of diary MET corrected for tau (0.12), phospho-tau (0.13), as well as diary MVPA corrected for HADS (0.13) showed a stronger deviation >0.1 . In all cases, there was (like for all other parameters) no significant zero order correlation between the physical activity parameters and the correcting variable (for tau: Fitbit MET, $\rho = 0.09$, $p = 1$, diary MET, $\rho = -0.4$, $p = 0.07$; for phospho-tau: Fitbit MET, $\rho = 0.05$, $p = 1$, diary MET, $\rho = -0.38$, $p = 0.92$; for HADS: Fitbit MVPA, $\rho = -0.24$, $p = 1$, diary MVPA, $\rho = -0.02$, $p = 1$) that could have indicated a causal relationship between these variables, and therefore supported the assumption of a systematic influence of the correcting variable in partial correlation analysis.

Discussion

We here present three different methods of physical activity assessment in a population with AD during a 6 months intervention study (Dementia-MOVE): (1) wearable fitness trackers, (2) diaries on daily activities and (3) questionnaires on physical activity. We aimed at comparing these methods in terms of their feasibility and reliability when study participants are affected by AD and therefore suggest a homogenization method in the presented study. We show that different physical activity assessment methods can be well homogenized when paying attention to inter- as well as intra-individual differences. In this context, one of the strengths of our study is that our study group is well-characterized and relatively homogenous due to our rigorous inclusion and exclusion criteria, resulting in a comparatively smaller sample size that still yields robust results, also supported by our previous power calculations. Therefore, all physical activity assessment methods showed a high compliance and acceptance rate during our 6 months intervention. MET and

MVPA scores from fitness trackers and diaries are highly overlapping, and their physical activity assessment independent of Alzheimer's pathology and cognitive state. An overview of the advantages and disadvantages of the different assessment methods and limitations is illustrated in Figure 3, for which we summarized eight categories, which are important to consider when trying to find the most suitable method for activity assessment. We therefore assigned a score between zero and ten (with zero = lowest score, and ten = highest score) based on our experience and estimation and then visualized the scores proportionally. The different assessment methods will be discussed in detail highlighting their strengths and limitations in the following sections.

The wearable tracker as a modern extension to physical activity monitoring in AD

Commercially available fitness trackers get more and more refined due to technological improvements, are meanwhile widely integrated into our daily life and are even used for health promotion and disease prevention (39–42). The reliability of wearable trackers has been evaluated before, pointing out a good validity of the devices' accelerometric data such as steps, and covered distance but also the heart rate (43), whereas the calculation of activity minutes or calorie consumption are still discussed to give heterogeneous results especially in the elder generation (44, 45). The advantage of this tracker is that it is small, affordable, wearable as a watch and usable without the need of extensive habits or without being cognitively demanding and therefore independent of AD-pathology. This is also reflected by our proven 100% compliance in wearing fitness trackers as supported by the tracker data. Still, taking these previous publications into account, our main parameter for comparison was the MET score generated out of the Fitbit's walking distance. We indeed registered deviating values for moderate and vigorous training intensity minutes when comparing Fitbit and diary data, however, the sum of both indicated as MVPA values were again strongly overlapping. This effect is presumably based on a differing distinction of physical activity intensity between both tools. Based on our results, the Fitbit had a lower threshold for classifying activities as vigorous intensity. It would be conceivable that the Fitbit has a higher sensitivity, as it is theoretically capable to incorporate not only MET values but also heart rate and personal data such as the age of the user

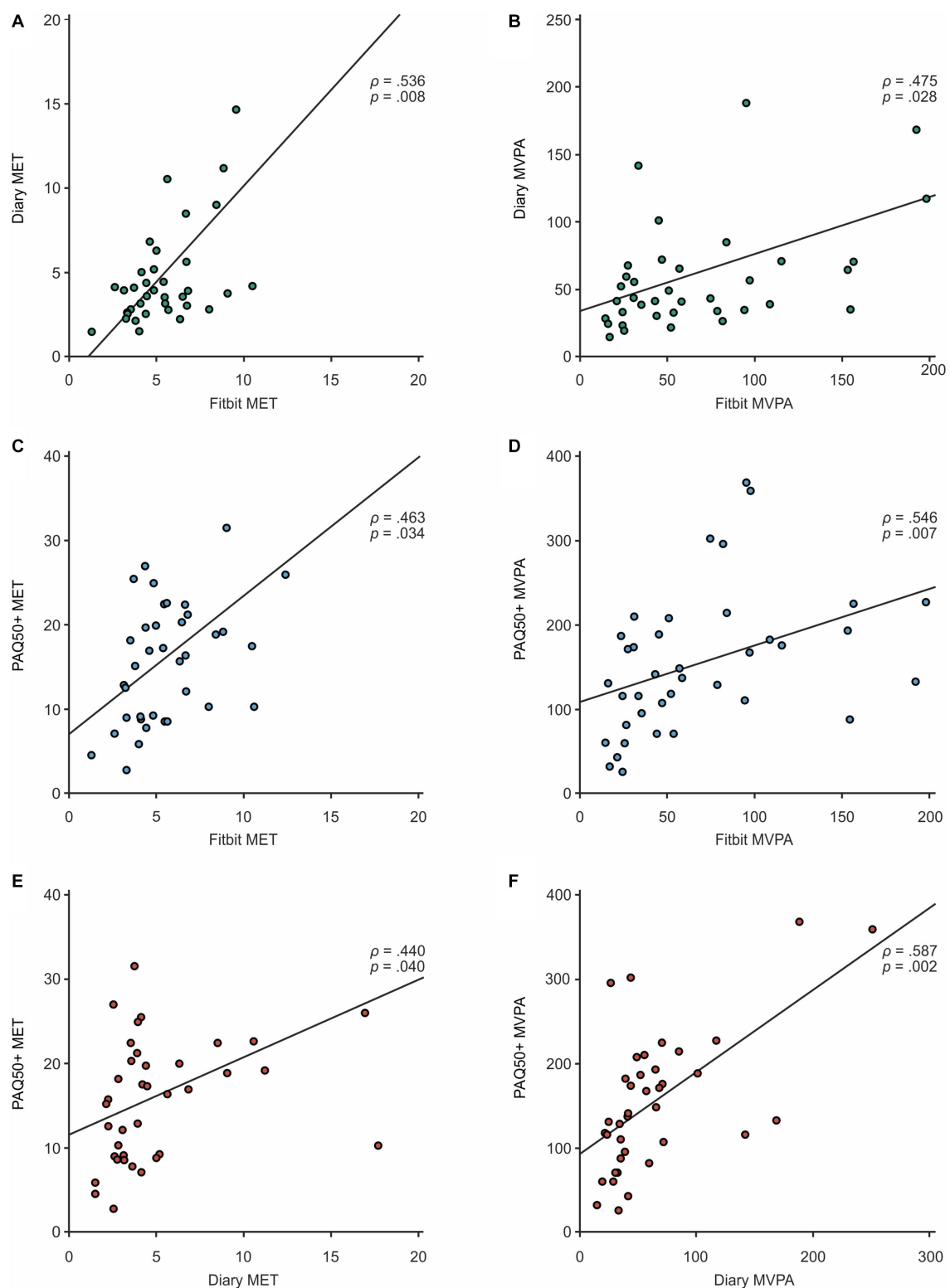


FIGURE 1

Correlation plot for comparison of MET and MVPA deriving from (A,B) Fitbit vs. diary (top), (C,D) Fitbit vs. PAQ50 (middle), and (E,F) diary vs. PAQ50+ (bottom).

into its analysis, yet Feehan et al. as well reported a tendency of the device to overestimate vigorous activity which is also reflected by our results (44). Further discrepancies were also detected when comparing

the activity calories of all three different measuring tools, again pointing to a fundamentally divergent calculation algorithm. Unfortunately, we cannot definitively answer these questions, as most

of the Fitbit's detailed analysis algorithms, and threshold values are subject to company secrecy, which is one of the largest minus points. Therefore, the usage of the summarizing MVPA next to the step count in intervention studies is recommendable. Due to the inaccuracies stated above the activity calorie consumption however should be a parameter considered with lower priority.

Concerning the applicability of wearable devices in an elderly population, we stated challenges with synchronization which could be solved by narrowing the span of the synchronization process and by integrating the smartphones of the participants and their

caregivers if available. This required a stronger involvement of the participants, which still led to the 100% compliance as mentioned before. In general, the experience in entrusting participants with these technical tasks under close instruction was positive, confirming the previously described large acceptability by older adults (46). Also worth mentioning is the high amount of additional information, such as sleep and vital parameters continuously measured by the device. However, the effort required for a continuous application for longer intervention periods, potentially taking months to years, would require a higher inclusion of the participants for regular synchronization and therefore a high availability of smartphones in this cohort, which is currently with more than 40% of smartphone users in the generation 65+ in Germany still in progress (47). With that in mind, an application of fitness trackers in long-term studies as an objective control can be a valuable option, especially when regular synchronization processes and closer follow-ups are performed. Yet, previous findings stated that also short measuring periods are sufficient to capture a ground physical activity level of older people, so even with short-term application, the information gain of wearable trackers can be valuable depending on the intervention design and overall objective (48). Furthermore, to our knowledge there has not been any previous intervention study in AD applying Fitbit wearable fitness trackers which we proved as feasible in the presented study.

Subjective physical activity assessment via diary is feasible in (early) AD

We established the physical activity diary in our study protocol to continuously keep track of the participants' dynamics in activity and to supervise protocol adherence over the course of the intervention. One of the main advantages of the diary is the flexibility in design, which allows a precise tailoring to the respective research question. Inaccuracies due to recall bias are reported for diaries, yet this source of error is minimized compared to questionnaires by entering activity information on a daily base (49). Integrating a physical activity diary in exercise study protocols also increased adherence in previous studies, which is underlined by a high compliance in our AD cohort, both in the intervention and the control group (50, 51).

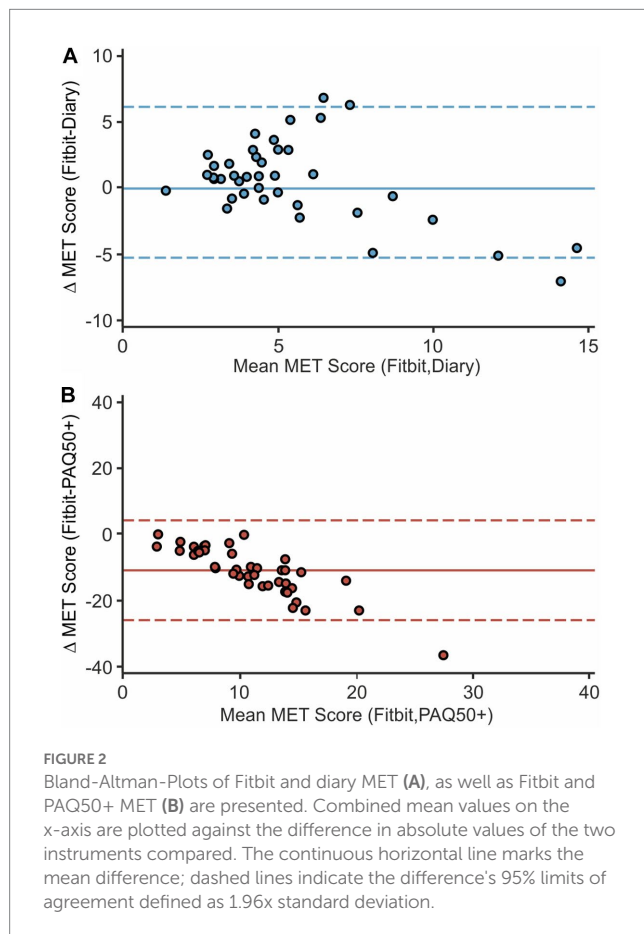


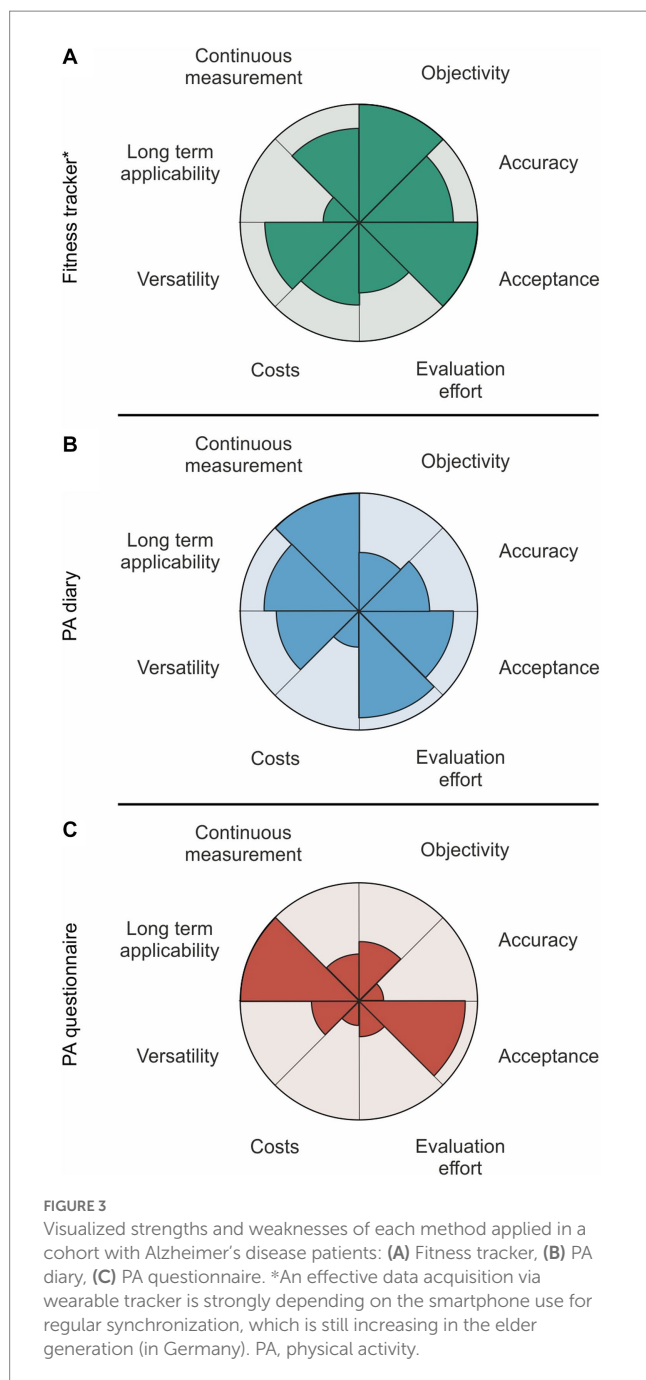
TABLE 3 Partial correlation analysis correcting for potential confounding factors.

Controlling variable	Fitbit MET vs. Diary MET	Fitbit MVPA vs. Diary MVPA	Fitbit MET vs. PAQ50+ MET	Fitbit MVPA vs. PAQ50+ MVPA
CSF Amyloid- β 1–42 ^a	0.505* (0.01)	0.400* (0.00)	0.467* (0.02)	0.526* (0.00)
CSF Amyloid- β 42/40-ratio ^b	0.531* (0.01)	0.405 (0.01)	0.495* (0.00)	0.514* (0.01)
CSF Tau ^a	0.601** (0.12)	0.400 (0.02)	0.495* (0.00)	0.519* (0.00)
CSF Phospho-tau ^a	0.576** (0.13)	0.385* (0.04)	0.485* (0.02)	0.517* (0.01)
MoCA	0.502* (0.06)	0.475* (0.00)	0.428* (0.08)	0.542* (0.01)
HADS	0.539** (0.01)	0.535* (0.13)	0.464* (0.00)	0.558** (0.02)
Education years	0.517* (0.04)	0.469* (0.01)	0.442* (0.05)	0.541* (0.01)

^an = 35/38 participants.

^bn = 34/38 participants.

Partial ρ correlation coefficients are indicated, together with the percentage difference from the uncorrected correlation analysis in brackets. *indicates $p < 0.05$, **indicates $p < 0.01$, respectively. CSF, cerebrospinal fluid; MoCA, Montreal Cognitive Assessment; HADS, Hospital Anxiety and Depression Scale; MET, metabolic equivalent of task; MVPA, moderate-to-vigorous physical activity (in minutes).



When comparing the data captured in the diary with the fitness tracker output, we registered a surprisingly strong concordance of the MET and MVPA mean values, which was not only reflected when comparing data of the matching recording days, but also of the whole intervention period reinforcing the equally good suitability for assessing the ground physical activity level of both methods. The further correlation and largely bias-free visualization in the Bland–Altman-Plot confirmed a high agreement among diary and tracker.

When examining our data for possible AD-related influencing factors, that may have biased our assessment, we found no significant association. This is particularly interesting, since even the cognitive state reflected by the MoCA score did not influence the correlation between the different assessment tools. There is previous literature pointing to a possible association between tau accumulation and subjective physical activity assessment, which was not clearly reflected in our sample (52).

This however has to be interpreted with caution, since CSF markers from our sample originated from the timepoint of diagnosis, which in most cases did not correspond with the intervention start (with CSF analysis performed in a range of a maximum time difference of 1954 days before intervention start to 189 days after intervention start). In this context, however, previous literature has pointed to only slowly progressing longitudinal changes in CSF markers in AD (53–55).

Especially as an addition to wearable trackers, the diary requires low effort and costs in the assessment period, making its use attractive for smaller intervention studies that cannot afford to supervise the tracker's measurement for an extended period of time. Still, precise instructions and a regular check for quality and compliance is crucial to guarantee good results from this method. A combination of both tools, as performed in our study, is also helpful to enable a further verification of the subjective diary data in the individual study cohort.

Structured questionnaires recommended under precise instructions

Based on their design, structured questionnaires can be a simple and short way to assess physical activity, which is why they are often applied especially in observational studies analyzing the influence of physical activity on cognitive health and AD disease progression (56, 57). Depending on the distinct questionnaire, they usually take only a few minutes to fill out and offer specified scoring routines that enable a fast and low-effort information gain (10). However, difficulties in assessing average physical activity details are well-described for short-term recall questionnaires, and seem to occur even more likely in people with cognitive impairment (12).

We stated an overestimation of physical activity by the study participants in the PAQ50+ compared to the Fitbit and the physical activity diary which was also reflected in the Bland–Altman-Plot, visualizing a negative difference of $MET_{\text{Fitbit-PAQ50+}}$ values for almost all participants. There was also a proportional trend in the graphic presentation with an increasing extent of overestimation for participants with a higher physical activity pointing to a generally rather reduced accuracy of the questionnaire. These results are supported by previous findings, showing that people with a higher activity level are more likely to over-report their physical activity (58). Furthermore, questionnaires are considered to be especially applicable for reporting vigorous activity, which can, in combination with memory recall problems, lead to an overestimation of physical activity (59–61). The design of the PAQ50+ to estimate the average weekly duration of different activities based on the last month was possibly challenging for many participants in our cohort due to their cognitive impairment. Eventually, a simplified design concerning the questionnaire's reference time-period (e.g., daily activity) might be more suitable for people having a hard time to remember their retrospective activities in intervention studies (62).

Concerning our correlation analysis, there was still an association of the PAQ50+ with the fitness tracker and diary assessment, which might indicate that the information entered in the questionnaire still follows a constant pattern with preserved proportionality despite the fundamental differences in absolute values, possibly enabling an examination of intra-individual physical activity dynamics. However, this alone is not sufficient to consider the PAQ50+ measurement reliable, at least based on the results of our cohort.

Altogether, the limited application of questionnaires in AD intervention studies should be considered, and the precise research question and the suitability of the questionnaire for the specific cohort need to be discussed. Special attention should be paid to understandable and simple instructions, when selecting an appropriate questionnaire for participants with cognitive impairment.

How to choose the right physical activity monitoring method and parameters in AD?

The decision on the assessment method for physical activity is *a priori* dependent on the objective and the study sample itself. We deliberately do not define a gold standard for our analysis since all three methods have different advantages and disadvantages: Fitness trackers can be used independently of the cognitive state of the user and are well accepted by the study participants. However, synchronization of data and therefore availability of corresponding tools, especially smart phones in elder generations need to be considered. In the absence of a smartphone, the collection and synchronization by the study team on a regular base can be related to a higher effort, whereas continuous synchronization assured by the participants' smartphones can enable longer and continuous periods of data collection, which has to be considered as a caveat in the planning phase of an intervention study.

For physical activity diaries, participants with AD need to be in a cognitive state comparable to our participants. Physical activity questionnaires can entail risks of overestimating physical activity due to insufficient recall on retrospective activity. Concluding from our results, fitness trackers and physical activity diaries are both feasible and recommendable, leading to a highly comparable estimation of physical activity in AD pathology and can be homogenized and compared as described above via calculation of MET and MVPA. As assessed parameters, it is recommendable to focus on MET, MVPA and on accelerometric data such as step count, and less on activity calories and different activity intensities which are less robust since these are dependent on different variables. Altogether, multimodal assessment of physical activity with a focus on most robust and replicable parameters can lead to an increased quality of exercise intervention studies in AD pathology and even other neurodegenerative diseases entailing cognitive decline, helping to gradually close the knowledge gap on how physical activity and (cardiorespiratory) fitness influence each other in the elder generation and how they mutually impact disease progression.

Data availability statement

The data supporting the conclusions of this article will be made available on reasonable request.

Ethics statement

The studies involving humans were approved by ethics committee of the University Hospital RWTH Aachen (EK 306/18). The studies were conducted in accordance with the local legislation and

institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AH, AC, and KR contributed to the conception and design of the study. AH supervised the study and the methodology. CH developed the database and performed the data management. SD performed the statistical analysis and wrote the first draft of the manuscript. SD, LH, and JP performed data acquisition. AK and his team supervised the sports program. All authors corrected and reviewed the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2023.1195694/full#supplementary-material>

References

- Li X, Feng X, Sun X, Hou N, Han F, Liu Y. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2019. *Front Aging Neurosci.* (2022) 14:937486. doi: 10.3389/fnagi.2022.937486
- Haeger A, Costa AS, Schulz JB, Reetz K. Cerebral changes improved by physical activity during cognitive decline: a systematic review on MRI studies. *NeuroImage Clin.* (2019) 23:101933. doi: 10.1016/j.nicl.2019.101933
- Santos-Lozano A, Pareja-Galeano H, Sanchis-Gomar F, Quindós-Rubial M, Fiuza-Luces C, Cristi-Montero C, et al. Physical activity and Alzheimer disease: a protective association. *Mayo Clin Proc.* (2016) 91:999–1020. doi: 10.1016/j.mayocp.2016.04.024
- Groot C, Hooghiemstra AM, Raijmakers PGHM, van Berckel BNM, Scheltens P, Scherder EJA, et al. The effect of physical activity on cognitive function in patients with dementia: a meta-analysis of randomized control trials. *Ageing Res Rev.* (2016) 25:13–23. doi: 10.1016/j.arr.2015.11.005
- Bisbe M, Fuente-Vidal A, López E, Moreno M, Naya M, de Benetti C, et al. Comparative cognitive effects of choreographed exercise and multimodal physical therapy in older adults with amnesic mild cognitive impairment: randomized clinical trial. *J Alzheimers Dis.* (2020) 73:769–83. doi: 10.3233/JAD-190552
- Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol.* (2014) 13:788–94. doi: 10.1016/S1474-4422(14)70136-X
- Cummings JL, Tong G, Ballard C. Treatment combinations for Alzheimer's disease: current and future pharmacotherapy options. *J Alzheimers Dis.* (2019) 67:779–94. doi: 10.3233/JAD-180766
- Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the lancet commission. *Lancet (London, England).* (2020) 396:413–46. doi: 10.1016/S0140-6736(20)30367-6
- van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med.* (2023) 388:9–21. doi: 10.1056/NEJMoa2212948
- Sylvia LG, Bernstein EE, Hubbard JL, Keating L, Anderson EJ. Practical guide to measuring physical activity. *J Acad Nutr Diet.* (2014) 114:199–208. doi: 10.1016/j.jand.2013.09.018
- Liyanage SI, Santos C, Weaver DF. The hidden variables problem in Alzheimer's disease clinical trial design. *Alzheimer's Dement (New York, N Y).* (2018) 4:628–35. doi: 10.1016/j.trci.2018.09.003
- Ainsworth B, Cahalin L, Buman M, Ross R. The current state of physical activity assessment tools. *Prog Cardiovasc Dis.* (2015) 57:387–95. doi: 10.1016/j.pcad.2014.10.005
- Breasail MÓ, Biswas B, Smith MD, Mazhar MKA, Tenison E, Cullen A, et al. Wearable GPS and accelerometer Technologies for Monitoring Mobility and Physical Activity in neurodegenerative disorders: a systematic review. *Sensors (Basel).* (2021) 21:8261. doi: 10.3390/s21248261
- Favela J, Cruz-Sandoval D, Morales-Tellez A, Lopez-Nava IH. Monitoring behavioral symptoms of dementia using activity trackers. *J Biomed Inform.* (2020) 109:103520. doi: 10.1016/j.jbi.2020.103520
- Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeblerlein SB, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* (2018) 14:535–62. doi: 10.1016/j.jalz.2018.02.018
- Abramson JH. WINPEPI updated: computer programs for epidemiologists, and their teaching potential. *Epidemiol Perspect Innov.* (2011) 8:1. doi: 10.1186/1742-5573-8-1
- Ries JD, Echternach JL, Nof L, Gagnon BM. Test-retest reliability and minimal detectable change scores for the timed "up & go" test, the six-minute walk test, and gait speed in people with Alzheimer disease. *Phys Ther.* (2009) 89:569–79. doi: 10.2522/ptj.20080258
- Åstrand P-O, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work. *J Appl Physiol.* (1954) 7:218–21. doi: 10.1152/jappl.1954.7.2.218
- Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x
- Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry.* (1982) 140:566–72. doi: 10.1192/bjp.140.6.566
- Herrmann-Lingen C, Buss U, Snaith RP. *Hospital anxiety and depression scale: HADS-D: deutsche Version; ein Fragebogen zur Erfassung von Angst und Depressivität in der somatischen Medizin.* Bern: Testdokumentation und Handanweisung Huber (2005).
- Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc.* (1982) 14:377–81. doi: 10.1249/00005768-198205000-00012
- Yu F, Kolanowski A. Facilitating aerobic exercise training in older adults with Alzheimer's disease. *Geriatr Nurs (Minneapolis).* (2009) 30:250–9. doi: 10.1016/j.gerinurse.2008.11.001
- Haeger A, Costa AS, Romanzetti S, Kilders A, Trautwein C, Haberl L, et al. Effect of a multicomponent exercise intervention on brain metabolism: a randomized controlled trial on Alzheimer's pathology (dementia-MOVE). *Alzheimer's Dement (New York, N Y).* (2020) 6:e12032. doi: 10.1002/trc2.12032
- Huy C, Schneider S. Instrument for the assessment of middle-aged and older adults' physical activity: design, reliability and application of the German-PAQ-50+. *Z Gerontol Geriatr.* (2008) 41:208–16. doi: 10.1007/s00391-007-0474-y
- Washburn RA, Smith KW, Jette AM, Janney CA. The physical activity scale for the elderly (PASE): development and evaluation. *J Clin Epidemiol.* (1993) 46:153–62. doi: 10.1016/0895-4356(93)90053-4
- Montoye HJ, Kemper H, Saris W, Washburn R. Measuring physical activity and energy expenditure. *Champaign Hum Kinet.* (1996):3–118.
- Harada ND, Chiu V, King AC, Stewart AL. An evaluation of three self-report physical activity instruments for older adults. *Med Sci Sports Exerc.* (2001) 33:962–70. doi: 10.1097/00005768-200106000-00016
- Sternfeld B, Goldman-Rosas L. A systematic approach to selecting an appropriate measure of self-reported physical activity or sedentary behavior. *J Phys Act Health.* (2012) 9:S19–28. doi: 10.1123/jpah.9.s1.s19
- Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc.* (2000) 32:S498–516. doi: 10.1097/00005768-200009001-00009
- Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc.* (2007) 39:1435–45. doi: 10.1249/mss.0b013e3180616aa2
- Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA.* (1995) 273:402–7. doi: 10.1001/jama.1995.03520290054029
- Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METs) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol.* (1990) 13:555–65. doi: 10.1002/clc.4960130809
- Germini F, Noronha N, Borg Debono V, Abraham Philip B, Pete D, Navarro T, et al. Accuracy and acceptability of wrist-wearable activity-tracking devices: systematic review of the literature. *J Med Internet Res.* (2022) 24:e30791. doi: 10.2196/30791
- Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet (London, England).* (1986) 1:307–10. doi: 10.1016/S0140-6736(86)90837-8
- Grouven U, Bender R, Ziegler A, Lange S. Comparing methods of measurement. *Dtsch Med Wochenschr.* (2007) 132:e69–73. doi: 10.1055/s-2007-959047
- Reiber H. Liguordagnostik: Labor und Diagnose. *Frankfurt, TH Books,* (2005)
- Zettl UK, Lehmitz R, Mix E. Klinische Liguordagnostik. Berlin, de Gruyter. (2005).
- Lubitz SA, Faranesh AZ, Selvaggi C, Atlas SJ, McManus DD, Singer DE, et al. Detection of atrial fibrillation in a large population using wearable devices: the Fitbit heart study. *Circulation.* (2022) 146:1415–24. doi: 10.1161/CIRCULATIONAHA.122.060291
- Natalucci V, Marmondi F, Biraghi M, Bonato M. The effectiveness of wearable devices in non-communicable diseases to manage physical activity and nutrition: where we are? *Nutrients.* (2023) 15:913. doi: 10.3390/nu15040913
- Ringeval M, Wagner G, Denford J, Paré G, Kitsiou S. Fitbit-based interventions for healthy lifestyle outcomes: systematic review and meta-analysis. *J Med Internet Res.* (2020) 22:e23954. doi: 10.2196/23954
- Lima FV, Kadiyala V, Huang A, Agusalá K, Cho D, Freeman AM, et al. At the crossroads! Time to start taking smartwatches seriously. *Am J Cardiol.* (2022) 179:96–101. doi: 10.1016/j.amjcard.2022.06.020
- Fuller D, Colwell E, Low J, Orychok K, Ann Tobin M, Simango B, et al. Reliability and validity of commercially available wearable devices for measuring steps, energy expenditure, and heart rate: systematic review. *JMIR Mhealth Uhealth.* (2020) 8:1–23. doi: 10.2196/18694
- Feehan LM, Geldman J, Sayre EC, Park C, Ezzat AM, Yoo JY, et al. Accuracy of Fitbit devices: systematic review and narrative syntheses of quantitative data. *JMIR Mhealth Uhealth.* (2018) 6:e10527. doi: 10.2196/10527
- St Fleur RG, St George SM, Leite R, Kobayashi M, Agosto Y, Jake-Schoffman DE. Use of Fitbit devices in physical activity intervention studies across the life course: narrative review. *JMIR Mhealth Uhealth.* (2021) 9:e23411. doi: 10.2196/23411
- Tocci FL, Morey MC, Caves KM, Deberry J, Leahy GD, Hall K. Are older adults ready for wireless physical activity tracking devices? A comparison of commonly used tracking devices. *J Am Geriatr Soc.* (2016) 64:226–8. doi: 10.1111/jgs.13895
- Bitkom. Welche der folgenden Geräte verwenden Sie aktuell zumindest hin und wieder? [Internet]. *Senioren in der digitalen Welt.* (2020):9. Available at: <https://de.statista.com/statistik/daten/studie/166326/umfrage/verbreitung-von-handys-und-smartphones-bei-senioren-in-deutschland/>
- Buckley C, Cavadino A, Del Din S, Lord S, Taylor L, Rochester L, et al. Quantifying reliable walking activity with a wearable device in aged residential care: how many days are enough? *Sensors (Basel).* (2020) 20:6314. doi: 10.3390/s20216314

49. Ndahimana D, Kim E-K. Measurement methods for physical activity and energy expenditure: a review. *Clin Nutr Res.* (2017) 6:68–80. doi: 10.7762/cnr.2017.6.2.68
50. Goldberg SE, van der Wardt V, Brand A, Burgon C, Bajwa R, Hoare Z, et al. Promoting activity, Independence and stability in early dementia (PrAISED): a, multisite, randomised controlled, feasibility trial. *BMC Geriatr.* (2019) 19:353. doi: 10.1186/s12877-019-1379-5
51. Cox KL, Cyarto EV, Ellis KA, Ames D, Desmond P, Phal P, et al. A randomized controlled trial of adherence to a 24-month home-based physical activity program and the health benefits for older adults at risk of Alzheimer's disease: the AIBL active-study. *J Alzheimers Dis.* (2019) 70:S187–205. doi: 10.3233/JAD-180521
52. Brown BM, Rainey-Smith SR, Dore V, Peiffer JJ, Burnham SC, Laws SM, et al. Self-reported physical activity is associated with tau burden measured by positron emission tomography. *J Alzheimers Dis.* (2018) 63:1299–305. doi: 10.3233/JAD-170998
53. Buchhave P, Blennow K, Zetterberg H, Stomrud E, Londo E, Andreasen N, et al. Longitudinal study of CSF biomarkers in patients with Alzheimer's disease. *PLoS One.* (2009) 4:e6294. doi: 10.1371/journal.pone.0006294
54. Vemuri P, Wiste HJ, Weigand SD, Knopman DS, Trojanowski JQ, Shaw LM, et al. Serial MRI and CSF biomarkers in normal aging, MCI, and AD. *Neurology.* (2010) 75:143–51. doi: 10.1212/WNL.0b013e3181e7ca82
55. Lleó A, Alcolea D, Martínez-Lage P, Scheltens P, Parnetti L, Poirier J, et al. Longitudinal cerebrospinal fluid biomarker trajectories along the Alzheimer's disease continuum in the BIOMARKAPD study. *Alzheimers Dement.* (2019) 15:742–53. doi: 10.1016/j.jalz.2019.01.015
56. Raji CA, Merrill DA, Eyre H, Mallam S, Torosyan N, Erickson KI, et al. Longitudinal relationships between caloric expenditure and Gray matter in the cardiovascular health study. *J Alzheimers Dis.* (2016) 52:719–29. doi: 10.3233/JAD-160057
57. Zhu J, Ge F, Zeng Y, Qu Y, Chen W, Yang H, et al. Physical and mental activity, disease susceptibility, and risk of dementia: a prospective cohort study based on UK biobank. *Neurology.* (2022) 99:e799–813. doi: 10.1212/WNL.0000000000000701
58. Cleland CL, Hunter RF, Kee F, Cupples ME, Sallis JF, Tully MA. Validity of the global physical activity questionnaire (GPAQ) in assessing levels and change in moderate-vigorous physical activity and sedentary behaviour. *BMC Public Health.* (2014) 14:1255. doi: 10.1186/1471-2458-14-1255
59. Ishikawa-Takata K, Tabata I, Sasaki S, Rafamantanantsoa HH, Okazaki H, Okubo H, et al. Physical activity level in healthy free-living Japanese estimated by doubly labelled water method and international physical activity questionnaire. *Eur J Clin Nutr.* (2008) 62:885–91. doi: 10.1038/sj.ejcn.1602805
60. Besson H, Brage S, Jakes RW, Ekelund U, Wareham NJ. Estimating physical activity energy expenditure, sedentary time, and physical activity intensity by self-report in adults. *Am J Clin Nutr.* (2010) 91:106–14. doi: 10.3945/ajcn.2009.28432
61. Ainsworth BE, Richardson MT, Jacobs DRJ, Leon AS, Sternfeld B. Accuracy of recall of occupational physical activity by questionnaire. *J Clin Epidemiol.* (1999) 52:219–27. doi: 10.1016/S0895-4356(98)00158-9
62. Farina N, Hughes LJ, Watts A, Lowry RG. Use of physical activity questionnaires in people with dementia: a scoping review. *J Aging Phys Act.* (2019) 27:413–21. doi: 10.1123/japa.2018-0031

Supplementary Table 1. Exemplary PA diary page translated into English language.

Intervention Week: _____ Calendar Week: _____ Name: _____

	xx/xx/xx	xx/xx/xx	xx/xx/xx	xx/xx/xx	xx/xx/xx	xx/xx/xx	xx/xx/xx	xx/xx/xx
	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	
<i>Supervised Exercise*</i>								
Home Sports – 30min 1x/week* (Which activity? How long?)								
<i>Training Cards – 15min 2x/week (Which card / exercise?)*</i>								
Complaints during exercise								
Perceived exertion during physical activity according to the Borg scale (0-10 points)								
Sleep (hours per night)								
Medication taken on demand								
Weight (1x/week without clothes)								

Other comments:

*Information presented in italic letters were only included in the PA diary for participants assigned to the intervention group

Supplementary Table 2. Spearman's rank correlation analysis of the three methods applied.

Variable	Fitbit vs. Diary		Fitbit vs. PAQ50+	Diary vs. PAQ50+
	record period	intervention period		
MET	.529** [.253; .740]	.536** [.230; .763]	.463* [.185; .685]	.440* [.106; .696]
Moderate Activity (min)	.155 [-.194; .462]	.309 [-.015; .582]	.515* [.223; .740]	.537** [.235; .753]
Vigorous Activity (min)	.130 [-.191; .429]	.340 [.001; .621]	.372 [.123; .565]	.556** [.310; .730]
MVPA (min)	.333 [-.023; .609]	.475* [.165; .692]	.546** [.282; .748]	.587** [.321; .776]
Activity Calories (kcal)	.462* [.156; .689]	.505* [.198; .725]	.459* [.123; .707]	.485* [.201; .703]

Spearman's ρ correlation coefficients are presented. 95% confidence intervals are computed via BCa-bootstrapping with 2000 samples. *indicates $p < 0.05$, **indicates $p < 0.01$. Correlation of Fitbit and diary data was carried out referring to means of recorded days and their matching diary entries only as well as means of the total intervention period.

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Erklärung § 5 Abs. 1 zur Datenaufbewahrung

Hiermit erkläre ich, dass die dieser Dissertation zu Grunde liegenden Originaldaten

- in der Klinik für Neurologie des Universitätsklinikums Aachen

hinterlegt sind.

Erklärung gemäß § 5 Abs. (1) und (2), und § 11 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, **Shari David**, an Eides statt, dass ich den wesentlichen Anteil an der Publikation: **David S**, Costa AS, Hohenfeld C, Romanzetti S, Mirzazade S, Pahl J, Haberl L, Schneider KM, Kilders A, Eggermann T, Trautwein C, Hildebrand F, Schulz JB, Reetz K, Haeger A. Modulating effects of fitness and physical activity on Alzheimer's disease: Implications from a six-month randomized controlled sports intervention. J Alzheimers Dis. 2025 Jan; Volume 103(2):552-569. doi: 10.1177/13872877241303764. geleistet habe. Die Anteile an der Arbeit waren wie folgt:

	Doktorandin S. David	Prakt. Betreuerin A. Häger	Doktormutter K. Reetz	Doktorandin 2 L. Haberl	Studienteam A. Costa J. Pahl	Weitere Ko-Autoren C. Hohenfeld S. Romanzetti S. Mirzazade K. Schneider A. Kilders T. Eggermann C. Trautwein F. Hildebrand J. Schulz	Summe (%)
Studienüberwachung	10	50	20	10	10	0	100
Studiendesign	5	50	25	5	10	5	100
Bereitstellung von Materialien	0	25	50	0	0	25	100
Probandenscreening	5	25	20	25	25	0	100
Rekrutierung (1h)	15	25	10	25	25	0	100
Terminvereinbarung (0.5h)	30	20	0	30	20	0	100
Studienaufklärung (1h)	0	75	0	0	25	0	100
Betreuung Sportintervention (1h)	30	10	0	20	40	0	100
Organisatorische Mitbetreuung Psychoedukationsprogramm (1h)	25	25	0	25	25	0	100
Durchführung Fitnessmessungen (1h)	30	5	0	20	45	0	100
Durchführung neuropsychologischer Testungen (2h)	25	10	0	25	40	0	100
Messhilfe MRT-Messungen (2.5h)	25	25	0	25	25	0	100
Datentransformation	25	50	0	0	0	25	100
Statistische Datenauswertung	85	15	0	0	0	0	100
Interpretation der Datenauswertung	70	20	10	0	0	0	100
Literaturrecherche	80	20	0	0	0	0	100
Verfassung des Manuskripts	100	0	0	0	0	0	100
Korrektur des Manuskripts	0	40	30	10	10	10	100

Zeitangaben geben Aufwand pro Probanden und Einheit an.

Aus diesem wesentlichen Anteil ergibt sich selbstverständlich die Stellung als Erstautorin.

Unterschrift der Doktorandin

Als Doktormutter und korrespondierende Autorin bestätige ich die Angaben von Frau **Shari David**.

Univ.-Prof. Dr. med. Kathrin Reetz

Ich schließe mich der Erklärung von Frau Univ.-Prof. Dr. Kathrin Reetz als Koautor an.

Erklärung gemäß § 5 Abs. (1) und (2), und § 11 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, **Shari David**, an Eides statt, dass ich den wesentlichen Anteil an der Publikation: **David S**, Hohenfeld C, Haberl L, Pahl J, Costa AS, Kilders A, Hildebrand F, Schulz JB, Reetz K, Haeger A. Physical activity monitoring in Alzheimer's disease during sport interventions: a multi-methodological perspective. Front Neurol. 2023 Sep; Volume 14:1195694. doi: 10.3389/fneur.2023.1195694. geleistet habe. Die Anteile an der Arbeit waren wie folgt:

	Doktorandin S. David	Prakt. Betreuerin A. Häger	Doktormutter K. Reetz	Doktorandin 2 L. Haberl	Studien- team A. Costa J. Pahl	Weitere Ko-Autoren C. Hohenfeld A. Kilders F. Hildebrand J. Schulz	Summe (%)
Studienüberwachung	10	50	20	10	10	0	100
Studiendesign	5	50	25	5	10	5	100
Bereitstellung von Materialien	0	25	50	0	0	25	100
Probandenscreening	5	25	20	25	25	0	100
Rekrutierung (1h)	15	25	10	25	25	0	100
Terminvereinbarung (0.5h)	30	20	0	30	20	0	100
Studienaufklärung (1h)	0	75	0	0	25	0	100
Betreuung Sportintervention (1h)	30	10	0	20	40	0	100
Organisatorische Mitbetreuung Psychoedukationsprogramm (1h)	25	25	0	25	25	0	100
Durchführung Fitnesstestungen (1h)	30	5	0	20	45	0	100
Durchführung neuropsychologischer Testungen (2h)	25	10	0	25	40	0	100
Messhilfe MRT-Messungen (2.5h)	25	25	0	25	25	0	100
Datentransformation	25	50	0	0	0	25	100
Statistische Datenauswertung	85	15	0	0	0	0	100
Interpretation der Datenauswertung	70	20	10	0	0	0	100
Literaturrecherche	80	20	0	0	0	0	100
Verfassung des Manuskripts	100	0	0	0	0	0	100
Korrektur des Manuskripts	0	40	30	10	10	10	100

Zeitangaben geben Aufwand pro Probanden und Einheit an.

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