Preserving Cognition, Quality of Life, Physical Health and Functional Ability in Alzheimer's Disease: The Effect of Physical Exercise (ADEX Trial): Rationale and Design

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Key Words

Alzheimer's disease · Clinical trial design · Cognition · Exercise · Intervention · Health-related quality of life · Physical function · β -Amyloid · Neuroimaging

Abstract

Background: Exercise is hypothesized to improve cognition, physical performance, functional ability and quality of life, but evidence is scarce. Previous studies were of short duration, often underpowered and involving home-based light exercise programs in patients with undefined dementia. The aim of the ADEX ('Preserving Cognition, Quality of Life, Physical Health and Functional Ability in Alzheimer's Disease: the Effect of Physical Exercise') trial is to establish whether aerobic exercise is effective in improving cognition as well as in reducing the prevalence of psychiatric symptoms among patients with Alzheimer's disease (AD). **Methods:** The ADEX study is a multicenter, single-blind, randomized trial with two arms: an intervention group attending 16 weeks of continuously supervised moderate-to-high intensity aerobic ex-

ercise and a control group receiving usual care. We plan to recruit 192 patients with mild AD. The primary outcome measure is change from baseline in cognitive performance at 16 weeks (as measured by the Symbol Digit Modalities test). **Conclusions:** To our knowledge this is the first large-scale controlled study to investigate the effects of supervised moderate aerobic exercise on cognition in patients with AD. Recruitment began in January 2012 and results are expected to be available in 2014. We summarize the methodological challenges we and other studies have faced in this type of complex multicenter intervention with unique challenges to study design.

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Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder worldwide, affecting more than 50% of patients with dementia. The clinical hallmarks of AD are progressive memory impairment and decreased

activities of daily living (ADL), ultimately leading to loss of independent living skills [1]. Current treatment for AD is symptomatic and can only temporarily slow down the progression of symptoms. New, potential disease-modifying treatment strategies have so far not demonstrated clinically relevant effects [2], underscoring the need for research in nonpharmacological treatments.

The relationship between physical activity and cognitive function is intriguing but remains undetermined [3, 4]. There are some indications that physical activity may protect against the occurrence of cognitive decline in nondemented subjects [5]. Additionally, meta-analyses of randomized clinical trials (RCTs) reported a modest effect on cognition from aerobic exercise in healthy older adults [6]. These results may, however, not be transferable to patients with AD.

It is encouraging that previous intervention trials have been able to improve physical function in patients with AD [7, 8] and other cognitive disorders [9, 10], but they did not include cognitive measures. Furthermore, in the study by Hauer et al. [9] exercise did not include endurance training and the endurance training intensity was not specified or lower than that planned in our study [7, 8, 10].

The underlying mechanisms for a potential effect of physical exercise on AD are unclear. According to current understanding of the pathophysiology of AD, cortical deposition of β -amyloid ($A\beta$) is considered central to the development of AD. In mice models of AD, physical exercise decreased $A\beta$ depositions in association with a positive effect on cognitive function [11, 12]. Brain-derived neurotrophic factor (BDNF) is important for long-term potentiation and formation of memory [13, 14]. Potential neuroprotective effects of physical exercise include an increase in BDNF [15] and enhanced hippocampal neurogenesis [16]. In healthy subjects the beneficial effects of physical exercise have been supported by studies showing increased memory performance and at the same time increased whole-brain and hippocampal volumes [17, 18], as well as increased activity in neural networks [19]. Moreover, cross-sectional studies in AD suggest that cardiorespiratory fitness is positively correlated to whole-brain [20] and medial temporal lobe [21] volume. Furthermore, an observational study in AD patients shows that greater cardiorespiratory fitness is associated with slowed progression of clinical symptoms and brain atrophy [22].

Only few intervention studies have investigated the underlying mechanisms of a potential effect and this is mainly examined in patients with mild cognitive impairment

(MCI) [23] or subjective memory complaints [24]. Furthermore, previous investigators have called for more hypothesis-driven research on changes in biomarkers [25].

Few RCTs have investigated the potential effect of physical exercise on the progression of cognitive decline. In general, most studies are on nursing home residents with AD and methodological issues restrict the conclusions which may be drawn from these studies [26, 27]. In nursing home residents with AD or unspecified dementia, some intervention studies show a positive effect of physical exercise on cognition [28, 29], whereas others show no effect [30–32]. In home-dwelling patients with AD, cognition has been the primary outcome in only one small study [33], which showed a positive effect of low-intensity physical exercise on tests of global cognition. In patients with MCI and in older subjects with memory complaints, physical exercise interventions have shown an effect on global cognition [34] and executive function, especially in women [23].

Some of the conflicting results from previous studies may arise from difficulties in comparing studies due to variations in outcome measures and exercise modalities. Methodological issues, such as small sample sizes and unsupervised intervention programs, may contribute to the discrepancies. Further, the effect of high-intensity exercise remains unknown since most studies have used low-intensity exercise programs [25]. Only a few studies assess depressive and behavioral symptoms in home-dwelling patients with AD [33, 35, 36] and in nursing home residents [8, 37, 38]. Quality of life has only rarely been an outcome parameter [34, 35].

As a result, we are launching a large, methodologically rigorous RCT entitled, ‘Preserving Cognition, Quality of Life, Physical Health and Functional Ability in Alzheimer’s Disease: the Effect of Physical Exercise (ADEX)’ with the aim to investigate the potential benefits of a moderate-to-high intensity aerobic exercise program on cognition, health-related quality of life, behavioral and psychological symptoms, and physical function in patients with mild AD. Further, mechanisms of the potential effects of physical exercise will be explored using fluid and imaging biomarkers. This report describes the rationale and design of the study.

Methods

Design

The ADEX study is a multicenter, single-blinded RCT with two arms – a control arm (receiving treatment as usual) and an intervention arm of 16 weeks (1 h, 3 times per week) of supervised

Table 1. ADEX inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1 NINCDS-ADRDA and DSM-IV criteria for AD	1 Participation in aerobic exercise program (moderate-to-hard intensity) more than twice weekly on a regular basis
2 50–90 years of age	2 Any musculoskeletal or joint problems that could interfere with completion of the study (significant joint problems, back pain or pain in arms and legs that provide problems with mobility in daily activities)
3 A score ≥ 20 on the MMSE	3 Male participants with all of the following risk factors, even if asymptomatic: smoking, arterial hypertension (systolic blood pressure >180) and hypercholesterolemia (>7 mM)
4 Brain imaging (CT or MRI) consistent with a diagnosis of AD	4 Major neurological (other than AD), cardiac or other medical diseases that constitute a contraindication to physical activity, i.e. severe aorta stenosis or cardiac rhythm disturbances. Stent operation or previous myocardial infarction is not an exclusion criteria if the participant has had a recent (within 3 months) normal exercise test
5 Caregiver with regular contact to the participant (more than once a month) who is also willing to participate in the study	5 Severe cerebrovascular disease judged from cranial CT or MRI
6 General good health allowing the participant to participate in physical exercise	6 Arterial hypertension defined as systolic blood pressure >180 and diastolic >100
7 At least 7 years of schooling and Danish speaking	7 Severe psychiatric disease, as well as alcohol or drug abuse within the last 2 years
8 Visual acuity and hearing that allow cognitive testing	8 Daily or almost daily intake of medications with known anti-cholinergic or adrenergic effect estimated to affect cognitive abilities; subjects treated with tricyclic antidepressants, antipsychotics (low doses of anxiolytics, e.g. oxazepam 15 mg/day, and nonbenzodiazepine hypnotics for the night are allowed)
9 At least 3 months of stable doses if the patient is receiving antidementia medication or mood stabilizing medication	
10 Informed consent	

moderate-to-high intensity aerobic exercise. Prior to initiation of the study, as recommended in the Medical Research Council's guidelines for complex interventions [39], an uncontrolled pilot study was carried out to ensure the acceptability, safety and feasibility of the intervention and study design.

Recruitment

Based on power calculations (see below), the goal is to recruit 192 community-dwelling participants of 50–90 years of age with mild AD who also have a caregiver willing to participate. Table 1 presents inclusion and exclusion criteria. Participants are being recruited across 8 sites in Denmark (Copenhagen, Slagelse, Roskilde, Odense, Aalborg, Aarhus, Svendborg and Glostrup).

Initiated in January 2012, the study is scheduled to end in 2014, at which point results will be made available. While the recruitment process will be continuous throughout the study period until the target has been reached, patients are randomized every 6 months in blocks of 5–10 per participating center. Recruitment will mainly be carried out among patients being followed in participating memory clinics. Moreover, information material is being distributed to general practitioners, private practice neurolo-

gists, other relevant specialists and primary care personnel. Potential participants are identified by screening patient records and checking suitability of the participants according to the inclusion and exclusion criteria. A screening log of all the patients deemed suitable for possible inclusion into the study is kept by each clinic.

Information and Screening

At the first visit, participants are given written and oral information. At the second visit (screening), after obtaining informed consent, inclusion and exclusion criteria are reviewed and thorough somatic and neurological examinations, including ECG and blood pressure measurements, are performed. A Mini Mental State Examination (MMSE) [40] is administered to ensure that participants meet the inclusion criteria with an MMSE score >19 . No upper limit of MMSE score is applied. Demographic data and detailed medical history, including actual medication, are obtained and a diagnosis of AD is confirmed according to the NINDS-ADRDA and DSM-IV criteria.

If the participant meets the inclusion criteria, a baseline visit is planned, at which time the baseline assessments will be carried out. A letter informing the participant's general practitioner about the

participation is sent encouraging him/her to refer the patient to the memory clinic if any study-related problems occur. Likewise, participants are encouraged to discuss any medical concerns with the research staff at their memory clinic.

Randomization and Blinding

Following baseline assessment, participants are randomly allocated to the exercise program or usual care group (control group) using a computerized random-number generator primarily in blocks of 8 (4 subjects randomly allocated to each group) to each participating center. If a center is unable to recruit 8 participants, a minimum of 5 participants is allowed. If a center recruits an uneven number of participants, skewed randomization is performed in favor of the intervention group. Allocation numbers are given over the phone and kept under sealed conditions by an investigator not directly involved in the project. Raters and testers are blinded to group allocation and previous test results; due to the nature of the study, however, the participants cannot be blinded. Prior to all assessments, participants are reminded not to disclose their group allocation to testers and raters.

All baseline data are collected prior to the randomization to prevent participants and staff from being biased due to group assignment.

Intervention

On the first day of the exercise program, participants and their caregivers are invited to a meeting where they are informed about the rationale for the study, the aerobic exercise program, appropriate exercise equipment (clothes and shoes), the etiology of overuse injuries and how to avoid them, how to react if exercise causes discomfort and what to do in the event of an overuse injury.

Exercise sessions are conducted in a group of 3–5 participants for 1 h, 3 times per week for 16 weeks. The purpose of the first 4 weeks of exercise is to accustom the participants to exercising (adaptation exercise). This period focuses on strength exercises, primarily of the legs (twice weekly) and an introduction to fitness exercise (once weekly). During the next 12 weeks, all exercise sessions focus on moderate-to-high intensity aerobic exercise (in total 3×10 min on ergometer bicycle, cross trainer and treadmill). Individually tailored, the exercise is designed to achieve an intensity of 70–80% of heart rate reserve. Heart rate and perceived exertion are monitored during all exercise sessions to ensure that the participants exercise with the intended intensity. Each session is supervised by the same experienced physiotherapist (who is different from the blinded tester performing the tests at baseline and at 4, 16 and 20 weeks).

Records of adherence to the program (attended sessions) are kept for each exercise session. Participants are not excluded due to adherence or compliance problems. Transportation to and from exercise sessions is reimbursed based on need in an effort to remove any barriers preventing participants and their caregivers from enrolling.

Control Group

The control group receives usual care for the first 16 weeks, followed by 4 weeks of supervised adaptation exercise for 1 h, 3 times per week. As for the intervention group, the first training session consists of an information meeting. The adaption exercise is also offered to the control group to strengthen recruitment and adherence to the program.

Fig. 1. Flowchart of the ADEX study. The estimated total number of participants is 192.

Usual care comprises planned outpatient visits (usually every 6 months) and access to memory clinic staff if medical or other needs necessitate contact. Moreover, participants are encouraged not to discontinue any participation in social or other activities.

Clinical Assessment Visits

The clinical assessments are comprised of two components: (1) cognitive/behavioral assessments lasting 1.5 h and (2) physical testing lasting 1 h. Participants are assessed at baseline, after 16 weeks (first follow-up) and after 20 weeks (second follow-up). In addition, physical performance is evaluated after 4 weeks of adaptation exercise (fig. 1). All assessment visits must be performed within 10 days before the first day of the intervention.

Cognitive Measures

The Symbol Digit Modalities test (SDMT) [41] is a simple substitution task using a reference key with nine different pairs of numbers and geometric figures that the participant must pair in a given time interval. Two scores are obtained in this study: (1) the number

of correct responses within the 90-second response time and (b) the number of correct responses within a 120-second response time.

The MMSE [40] is used as a screening instrument for global cognitive function. In the Alzheimer's Disease Assessment Scale – Cognitive Section (ADAS-Cog) recall test [42], the participant reads a list of 10 words and is asked to recall as many words as possible directly thereafter. The procedure is repeated 3 times. An *immediate recall score* (total number of correct words recalled on the 3 trials) and a *delayed recall score* (number of correct words recalled after 10 min) are recorded. Verbal fluency is evaluated based on two parts, category and lexical fluency. To assess category fluency, the category 'animals' is used. The score for this test is based on the number of different animals provided in 1 min. Lexical fluency is assessed with the letters F, A and S. For each letter, there is a 1-min response time. A *total lexical score* is the sum of the scores obtained on the 3 subtests. The Stroop Color and Word test [43] consists of three different parts (three different pages, each with 100 items). For each part, there is a 45-second time limit. Participants are asked to read the items as quickly as possible and then stopped if they make any errors. On the word page, the words 'green', 'red' and 'blue' are printed in black ink. The color page consists of 100 items all written as XXX and printed in red, green or blue. On the color word page, the names of the colors are printed in a different color than that which the word spells, i.e. the color and the word do not match. Each page is preceded by a reminder on what to do to minimize memory load. The score for each part is the number of words the participant can read in 45 s.

Questionnaires

The Neuropsychiatric Inventory (NPI) [44] is a well-established assessment of 12 different behavioral and psychological symptoms common in AD. The caregiver rates each symptom according to the frequency and severity. The Danish validated version is used [45]. The score (frequency times severity) for all items in total, as well as subitems (depression, anxiety, aggression, irritability and apathy) will be used.

The Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) scale [46] uncovers 23 ADL items by interviewing the caregiver. It includes more complex ADL for the assessment of mild AD such as reading books or magazines, leisure activities and household chores. The severity of any depressive symptoms is rated using the Hamilton Depression Rating Scale – 17 items (HAMD-17) [47] by interviewing the participant. Higher scores indicate more severe symptoms.

Two questionnaires are administered to both participant and caregiver, the EuroQol-5D-5L (EQ-5D), including EuroQol Visual Analogue Scale (EQ-VAS) scale [48] and Physical Activity Scale for the Elderly (PASE) [49]. The EQ-5D and EQ-VAS are employed for measuring health-related quality of life. They consist of a weighted sum of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, which provides a simple descriptive profile and a single index value for health status (VAS score).

PASE is administered by interview at baseline to assess the self-reported level of physical activity (household and leisure activities) of the participant prior to the baseline tests. Both participant and caregiver are interviewed.

Furthermore, exercise self-efficacy is assessed with the Exercise Self-Efficacy Scale by asking participants how confident they are about exercising under certain adverse conditions [50].

The research staff performing the cognitive tests and questionnaires (raters) are blinded to group assignment and their only role in the study is to perform assessment before and after exercise.

To ensure uniformity of the cognitive and questionnaires assessment, all raters have to complete a 1-day course led by an experienced neuropsychologist and an experienced psychiatrist. Training of the raters is repeated annually to standardize the assessment.

Physical Measures

All participants perform the following physical tests at baseline and at 4, 16 and 20 weeks (fig. 1). The 6-min Astrand Cycle Ergometer test (Monark Ergonomic 839E; Monark Exercise AB, Sweden) estimates the maximal oxygen uptake based on age, body weight and the workload, and average heart rate during the last minute of the test [51]. Functional performance tests include the Timed Up and Go (TUG) test [52], the 30-second chair stand test (the number of full stands in 30 s with arms folded across the chest from a standard chair) [32], the timed 10-min walk test (usual speed) [53] and the timed 400-meter walk test (fast speed) [54]. In addition, dual task performance is measured with the timed 10-min walk test combined with naming the months backwards and counting backwards from 50, respectively [53].

A subgroup of subjects perform additional tests at baseline and at 16 and 20 weeks to assess the following: (1) motor learning using the Rotary Pursuit test (Photoelectric Rotary Pursuit Model 30014C; Lafayette Instrument Europe, UK) [55]; (2) handgrip strength in each hand using a Jamar® dynamometer (Lafayette Instrument Europe) [56]; (3) maximal isometric knee extension strength at an angle of 90° of knee flexion (0° = full extension) using a handheld dynamometer (Lafayette Manual Muscle Testing System, Model 01165; Lafayette Instrument Europe) [57], and (4) maximal single leg extensor power using a Nottingham Leg Extensor Power Rig® (Medical Engineering Unit, Queen's Medical Centre, Nottingham University, UK) [58]. A graded cycle ergometer exercise test with simultaneous recording of the ECG is carried out to determine maximal oxygen uptake (VO₂ peak) using a pedaling frequency of 60 RPM on the Monark cycle ergometer and incrementally increasing load to exhaustion. The test is performed with a mask for measurement of maximal oxygen uptake by indirect calorimetry. Expired gases are collected online and analyzed with a metabolic measurement system (Jaeger, Master Screen CPX vers.5.21, Cardinal Health, Germany). A respiratory exchange ratio >1.10 indicates a valid test [59].

The research staff performing the physical tests (testers) attend a 1-day course on standardization of the physical tests led by an exercise physiologist and the principal physiotherapist investigator. In addition, they receive an instructional video of the tests and a visit by the principal physiotherapist investigator to ensure good quality of test procedures at each of the sites. The physiotherapists who deliver the exercise intervention (trainers) attend a 2-day course on the exercise program led by an exercise physiologist and the principal physiotherapist investigator. They are also visited by the principal physiotherapist investigator to ensure that the exercises are performed at each of the sites according to the protocol. The intervention is documented and standardized but individually tailored to each participant. New testers and trainers enrolled during the study will attend an individualized course led by the principal physiotherapist investigator.

Blood Samples, Cerebrospinal Fluid and Imaging

A panel of fluid biomarkers is measured to monitor the effects of physical exercise on pathology associated with AD. Blood samples (whole blood, plasma and serum) are collected from all participants at baseline and at first follow-up and stored in a central biobank.

A subgroup (up to 48 participants) will undergo magnetic resonance imaging (MRI), lumbar puncture and A β -PET (¹¹C-PiB-PET) at baseline and first follow-up. This subgroup also has to perform the additional physical tests at baseline and at 16 weeks as described above. Lumbar puncture is performed at the screening visit and MRI/PET is done within 2 months of the start and at the end of the 16-week intervention. Biomarkers specific to pathology in AD (A β in cerebrospinal fluid, CSF, and plasma, phospho-tau and neprilysin in CSF) as well as biomarkers of downstream processes such as neural degeneration (CSF-tau) are analyzed. Moreover, to further elucidate the underlying mechanisms that may mediate a beneficial effect of physical exercise on AD, BDNF, markers of insulin and glucose metabolism (glycosylated hemoglobin, HbA1C), inflammation (IL-1 and IL-6, and TNF α), hormones, cholesterol and triglycerides are measured in the blood.

Outcome Measurements

The primary outcome measure is change from baseline at 16 weeks in the SDMT score (120 s). The following tests (all change from baseline to week 16) are secondary cognitive outcome measures: ADAS-Cog recall test, verbal fluency, Stroop Color and Word test and MMSE. Additional secondary measures include changes in physical parameters, patient-reported health-related quality of life (EQ-5D and EQ-VAS), ADL (ADCS-ADL) and behavioral and depressive symptoms (table 2).

Adverse Event Reporting

Adverse events are recorded in the case report form. The protocol distinguishes between adverse events that may be directly attributable to the study interventions and the monitoring of adverse events not attributable to the study. Serious adverse events are reported within 24 h to the principal investigator. An independent safety committee consisting of a cardiologist and an orthopedic surgeon surveys the study, evaluates serious adverse events and performs a midterm interim analysis of adverse effects to evaluate safety issues that may warrant termination of the study. Medications and changes in medications during the study period are also registered.

Surveillance and Monitoring

Data monitoring is done according to the Medical Research Council [39] guidelines. Data from all centers are collected and monitored continuously by an investigator not directly involved in the project and blinded to the allocation group. The monitor also visits all centers annually.

Health Economic Analysis

Costs related to the intervention are calculated based on the expenses associated with exercise instruction and support, the time spent by participants and relatives, transportation costs and the participants' use of health care services. Cost-effectiveness (cost per quality-adjusted life year) is estimated from these cost calculations combined with changes in EQ-5D-5L scores over time

during the observation period. Costs involved in the use of health care services by participants and relatives are estimated from national administrative health registries.

Sample Size

Primary and secondary outcome changes from baseline at 16 weeks will be analyzed in the intent-to-treat population as well as in the per-protocol population. Based on the SDMT data from a previous study of aerobic exercise in patients with MCI [23], 154 subjects must be included ($\alpha = 5\%$, $\beta = 20\%$) to identify a minimal clinically relevant difference (minimal relevant difference, MIREDIFF) set at 5 points on the SDMT (typical mean values in mild AD: 50–60). With 192 subjects (24 per center on average), the present study will be able to demonstrate or reject a clinically meaningful effect on the primary endpoint if a dropout rate of 20% is assumed.

This sample size also makes it possible to detect clinically relevant differences in some important secondary outcomes: 126 subjects must be included ($\alpha = 5\%$, $\beta = 20\%$) to identify an MIREDIFF set to 6 points (equals 10%) in the EQ-5D-5L index score completed by caregivers (typical average values in mild AD: 60–70) [60]. Further, 50 subjects must be included ($\alpha = 5\%$, $\beta = 20\%$) to find an MIREDIFF of 5 ml/(kg·min; equals 15%) in the VO₂ max measured with the Astrand cycle ergometer test [61].

Data analysis will be corrected for multiple testing when necessary.

Ethics

The study is approved by the Danish National Committee on Biomedical Research Ethics, reference number H-3-2011-128 and by the Danish Data Protection Agency (J No. 30-0718). Even though exercise has not been established to be effective in the treatment of AD, its association with general health benefits is well accepted. As the duration and intensity of the exercise needed for a clinical effect is unknown, we find it ethically acceptable to offer all participants the opportunity to participate in an exercise program for either 4 or 16 weeks. Previous exercise intervention studies in patients with cognitive dysfunction and with similar exercise intensity as in our study report a very low incidence of adverse events [23, 34]. Therefore, we consider the potential benefits of the intervention to outweigh the risks associated with participation in our study.

Discussion

To our knowledge, this is the first large-scale RCT to investigate physical and cognitive effects of continuously supervised moderate-to-high intensity aerobic exercise in home-dwelling patients with an established diagnosis of mild AD. Depending on the results, this study could stimulate the development of community-deliverable moderate-to-high intensity aerobic exercise programs accessible for all patients with mild AD. The ADEX study is designed to overcome some of the methodological and design-related problems seen in previous studies. Because complex interventions of this kind present unique

Table 2. Outline of the assessments and timelines of the ADEX study

	Screening	Baseline (0 weeks)	Physical test (4 weeks)	First follow-up (16 weeks)	Second follow-up (20 weeks)
<i>Assessment tools</i>					
Demographics, medical history and medication	X			X	X
Blood samples	X			X	
<i>Cognitive tests</i>					
SDMT ¹		X		X	X
MMSE	X	X		X	X
ADAS-Cog recall test		X		X	X
Verbal fluency test (category and lexical)		X		X	X
Stroop Color and Word test		X		X	X
<i>Questionnaires</i>					
EQ-5D and EQ-VAS		X		X	X
Hamilton Depression Rating Scale 17 items (HAMD-17)		X		X	X
PASE		X			
<i>Caregiver-rated questionnaires</i>					
ADCS-ADL scale		X		X	X
NPI		X		X	X
EQ-5D and EQ-VAS		X		X	X
PASE		X			
<i>Physical tests and questionnaires</i>					
Height, weight		X	X	X	X
Exercise Self-Efficacy Scale (questionnaire)		X	X	X	X
Astrand Cycle Ergometer test for estimating VO ₂ max		X	X	X	X
TUG test		X	X	X	X
Timed 10-meter walk test		X	X	X	X
Timed 10-meter dual-task test		X	X	X	X
Timed 400-meter fast walking test		X	X	X	X
30-second chair stand test		X	X	X	X
<i>Assessment tools for subgroup</i>					
<i>Imaging and biomarkers</i>					
MRI		X		X	
Aβ-PET (¹¹ C-PiB-PET)		X		X	
CSF		X		X	
<i>Supplementary physical tests</i>					
Motor learning (rotary pursuit)		X		X	X
Handgrip strength		X		X	X
Maximal isometric knee extension strength		X		X	X
Maximal single-leg extensor power		X		X	X
Maximal oxygen uptake (VO ₂ peak)		X		X	X
For a more detailed description of the tests, see the following sections in the main body of text: Cognitive Measures, Questionnaires and Physical Measures.					
¹ Primary outcome.					

challenges to study design, piloting was undertaken to optimize the exercise program. In the pilot study, which comprised just 2 weeks of adaptation exercise, patients and caregivers reported that the subsequent first couple of weeks of the aerobic exercise were too challenging. As

a result, the design has been adapted to include 4 weeks of adaptation. No serious adverse events related to the exercise were experienced during the pilot study. Moderate-to-high intensity aerobic exercise was selected since previous studies in healthy older adults show that aerobic

exercise clearly benefits cognition (spatial memory) and hippocampal volume compared to resistance exercise [17]. Whether these findings in healthy subjects are transferable to home-dwelling patients with AD is uncertain.

Since low sample size and high dropout rates contribute to insufficient power in many other RCTs [26], one of our primary priorities is to promote recruitment and adherence. Chosen due to practical considerations, group exercise is the most cost-effective way to implement supervised exercise, but we also believe that the social interaction has a positive effect on adherence and participation. Other approaches involve reimbursement of transportation and a 4-week adaptation exercise period for the control group after the assessment of the outcome measures. Supervised individually, tailored aerobic exercise provides benefits in terms of objectivity and flexibility, since the individual intensity can be assessed in data analyses. This also means that participants need not be excluded unless participation and intensity drops to negligible levels.

Selection bias means that it is only possible to investigate the effect of moderate-to-high intensity aerobic exercise in a selected population of patients with AD. In essence this means that our study is an efficacy study rather than an effectiveness study. A logbook of participants not meeting inclusion criteria or not willing to participate will be kept to help identify the characteristics of patients who may benefit more from a different type of exercise intervention and to support future implementation in a broader group of patients with AD. However, to investigate the potential effect of exercise on AD, examining a well-defined homogenous group of patients is necessary. Clustering effects cannot be ruled out in a design involving 8 different memory clinics and 8 different exercise facilities with different staff. To minimize clustering effects, all raters, trainers and testers undergo regular and extensive training in standardized procedures throughout the study period. Although estimating clustering effects a priori is possible, as is adjusting sample size calculation accordingly, we have chosen not to do so since reliable estimates were not available. However, post hoc analysis to test for clustering effects will be performed and taken into consideration in the statistical analyses if such an approach is deemed appropriate.

In order to explore the underlying pathophysiology of a potential effect of physical exercise in AD, biomarkers are collected in a subgroup of participants. A limitation of the substudy on CSF and PET A β biomarkers is the duration of the exercise program. Recently, anti-A β monoclonal antibody treatment was shown to reduce cortical ¹¹C-

PiB retention over 78 weeks [62], which means the time window in our study may be too short to show an effect on AD pathology. Extending the exercise program beyond 16 weeks, however, was not considered feasible.

In summary, this rigorously conducted RCT will contribute to evidence regarding the potential effects of a supervised program of physical exercise for home-dwelling patients with AD. If the current exercise protocol should prove to be successful, exercise could compliment medical treatment.

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