FINAL REPORT

AAP Handicap et perte d'autonomie session 4

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Effects of a long-term exercise program on functional ability in people with dementia living in nursing homes: a cluster randomised controlled trial. The LEDEN study.

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Important Note.

For the presentation of this Final Report we opted, first of all, to introduce the ***protocol*** *of the LEDEN study as we designed it and, then, the* ***main results*** *with potential deviations from the protocol. Although this presentation may have repetitive information, it has the advantage of fully informing readers about the procedures adopted in the LEDEN study. Regarding the main findings of LEDEN, we have thoroughly analysed the effects of LEDEN's interventions on the main outcome measure (ie, functional ability) as well as on the following secondary outcome measures: cognitive function (mini-mental state examination) and physical performance, including gait speed and the Short Physical Performance Battery. Analyses on the remaining secondary clinical outcome measures (ie, pain, neuropsychiatric symptoms, and nutritional status) were only explored preliminarily for this Final Report and were included herein as Preliminary Results; these results must still be confirmed after a thorough examination. Health economic data has not been analysed yet and, therefore, will not be reported hereafter; analyses of such data is foreseen for December 2016 – February 2017.*

Please, note that the results of LEDEN are still under review for publication in scientific journals. In other words, the results presented herein were not yet published and should, therefore, be seen as a working material (still confidential).

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Research Protocol[1]

Rationale, Methods and Materials, and Timetable

Introduction

Dementia is a common condition in late life[1-3]; the prevalence of dementia is expected to markedly rise in the coming decades.[3,4] Dementia burden has increased in the last two decades,[5] including in terms of increased health costs.[6] Of particular importance is the fact that dementia increases the risk of developing functional limitations and disability;[7-9] therefore, the maintenance of optimal levels of functional ability is a crucial aspect of the healthcare of people with dementia (PWD).[10] Although dementia cannot be reversed, evidence suggests that disability in activities of daily living (ADL) can be delayed[11] and quality of life enhanced by appropriated interventions. Anti-dementia drugs in most RCTs testing drug effectiveness against placebo proved to have modest[12-15] or no[16-21] effects on ADL function in PWD. Therefore, developing safe and effective non-pharmacological interventions aiming at delaying the progression of declines in functional ability, particularly among institutionalised, often disabled PWD, is an urgent need worldwide with important public health implications.

Among the potential interventions for PWD living in the institutional setting, physical exercise, ie, planned, structured, repetitive, and purposeful physical activity, constitutes a promising intervention that has received increased attention in the last years. Exercise has been found to improve functional ability, physical function, neuropsychiatric symptoms (particularly depression), and even cognitive function (although the clinical relevance of this latter benefit is questionable) in PWD. The recent Cochrane review and meta-analysis by Forbes et al.[11] on exercise for PWD found that people who exercised, compared to controls, improved their ability to perform ADLs and their cognitive function; however, the heterogeneity across the studies entered into that meta-analysis was high, which preclude any solid conclusion to be drawn. Another Cochrane review and meta-analysis[22] on the benefits of

[1] The protocol was published at https://clinicaltrials.gov/ct2/show/NCT02444078

The following paper was published: *de Souto Barreto P, Denormandie P, Lepage B, Armaingaud D, Rapp T, Chauvin P, et al. Effects of a long-term exercise programme on functional ability in people with dementia living in nursing homes: Research protocol of the LEDEN study, a cluster randomised controlled trial. Contemp Clin Trials. 2016;47:289–95.*

physical therapy for long-term care residents showed that exercise improved ADL function and physical function (eg, walking speed). Although the target population was not composed only of PWD, this meta-analysis studied residents of long-term care facilities, institutions where the prevalence of dementia is very high. Our research team has conducted a systematic review and meta-analysis about exercise effects on neuropsychiatric symptoms in PWD (Unpublished data. Study protocol[23] was registered in PROSPERO database). Our main finding was that exercise significantly reduced depressive symptoms in PWD; while exercise tended to reduce global levels of neuropsychiatric symptoms, the analysis did not reach statistical significance.

Although research in PWD using behavioural interventions and performed in nursing homes (NH) presents non-negligible methodological advantages (eg, interventions being developed in the life space of the study participants, research monitoring may be facilitated and adherence rates probably improved, easy access to a large number of PWD and disabled people), very few high, and even moderate, quality exercise RCTs were developed in institutionalised PWD.[24] Most RCTs in NH did not apply cluster-randomisation,[22] which means that contamination between research's arms may not be excluded; to avoid contamination,[25] cluster-randomisation in RCTs using behavioural interventions is highly warranted. Furthermore, the benefits of group-based exercise (ie, the majority of exercise RCTs in NH are performed in group) may be partly dependent on the socialisation promoted through any group-based intervention. To date, exercise RCTs have used usual care as a comparator group or operationalised a socially active-control group through "light" and little structured interventions, such as social visits[26,27] or causal conversations.[28,29] To the best of our knowledge, no exercise RCTs in institutionalised PWD used structured social/recreational activities as comparators (see the review by Forbes and colleagues for further details on comparators).[10] Therefore, we designed the LEDEN study to fill in the above mentioned gaps. LEDEN is a cluster-randomised pilot study with the main objective of examining the effects of a 6-month exercise training, compared with a 6-month structured social/recreational activity, on the ability to perform ADLs in PWD living in NHs. Secondary objectives are to investigate if changes on ADLs performance remain in 3- and 6-month postintervention follow-ups, and the effects of the interventions on participants' physical function, incident falls and fractures, neuropsychiatric symptoms, pain, nutritional status and use of psychotropic drugs. We will also investigate the cost-effectiveness of the interventions. The main hypothesis of the LEDEN study is that exercise training delays the declines in functional

ability (ADL performance) in PWD, such a positive effect being independent of the socialisation aspect related to group-based activities.

Methods and Analysis

The reporting of this protocol is based on the guidance provided by the SPIRIT Statement.[30]

Study Design

LEDEN is a cluster-randomised controlled pilot trial composed of two research arms: exercise training group (experimental group) and a social/recreational activity group (control group). All participating NHs are located in France. The total duration of the study is 12 months, being six months of intervention plus six months of observational follow-up.

Eligibility criteria

The sole inclusion criterion for the selection of NHs is that the NH staff volunteers to participate in LEDEN. For patients, inclusion criteria are: confirmed diagnosis of Alzheimer's disease, vascular or mixed dementia according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); mini-mental state examination (MMSE) ≤ 20 (out of 30); age ≥ 65 years-old; living in one of the participating NHs for at least 3 months at the moment of baseline measurements; to be able of walking at least 4 meters (with walking devices if needed but without human assistance); to be able to rise from a chair without help or with minimal human assistance. Exclusion criteria are: MMSE > 20 (out of 30); terminal illness with life expectancy less than 6 months; diagnosis of Parkinson's disease; diagnosis of dementia with Lewy bodies; unstable cardiovascular condition or any other health condition that might be deteriorated by physical exercise; planned transfer from the NH to another NH or to home or to surgery during the 6-month period of intervention; already participating in physical exercise ≥ 2 times/week in the last 2 months prior to the date of baseline assessment.

Exercise interventionists will be professional exercise instructors with a 3-year university diploma (undergraduate studies) in Science and Techniques of Physical Activity and Sports (from the French term *STAPS*). All exercise instructors will already have experience in working with patients in the NH setting, particularly PWD patients. As for exercise interventionists, interventionists for the control group will already have experience in working with institutionalised older adults, particularly PWD patients.

Interventions

The interventions in the LEDEN study will be added to already existing activities in the NHs. Therefore, participants meeting study inclusion/exclusion criteria will not be asked to stop their usual activities. However, once enrolled in the LEDEN study, participants engage to not participate to another RCT during the whole duration of LEDEN, ie, 12 months. Participants can, however, participate in observational studies simultaneously to their participation in LEDEN if the observational study is supposed not to affect the outcome measures of LEDEN, particularly, functional ability**.**

Exercise programme (experimental group)

Exercise sessions will ideally be done in groups of three-to-eight persons to facilitate socialisation among participants and to allow the instructor to guide participants closely; although being a group-based exercise program, participants will be guided and the exercises will be adapted in an individual basis, which may increase adherence and compliance rates.[31] The exercise training will take place in the NH, twice weekly, 60 minutes per session (session duration can be shorter in the first weeks of intervention according with participants' physical capacity), during 6 months. Interval between two exercise sessions will be of at least 48 hours. The exercise program will be a multicomponent training, with exercises specifically developed to improve participants' flexibility, coordination and balance, muscle toning, and cardiorespiratory capacity. All exercise sessions will be accompanied by music. Exercise intensity targeted is moderate; exercise progression will be set individually and according to participants' physical and cognitive (ie, comprehension of the instructions) abilities. Although each exercise session may be modified by the exercise instructor according to participants' capabilities and interests, an ideal exercise session would be as follow:

1) First, participants execute 10 minutes of range of motion and a few light callisthenic exercises (for improving flexibility and preparing participants for the next exercises). The exercise instructor will establish a motivating atmosphere by helping participants to make the movements correctly and then providing positive feedback for each person individually; this interaction between instructors and participants is a key factor to increase exercise compliance and adherence, as well as to motivate participants to improve their engagement at each single session of exercise.
2) After that, participants do 10 minutes of coordination/balance exercises. Since sitting, standing, and initiating walks are commonly associated to falls,[32] we will focus on activities that explore these physical actions such as rising from a chair safely and short walks with direction changes.

3) Then, participants perform 10 to 15 minutes of muscle strength training. For this, weight-bearing exercises (for the lower-body) and light hand-held materials (for the upper-body), including therabands, may be used. The number of repetitions will vary according to the physical outcome (ie, developing muscle strength, power or endurance) and participants' physical capacity. For example, rising from a chair can constitute an extremely difficult task for some participants: 1 repetition for improving muscle strength would be a challenging goal for such a person, at least in the beginning of the exercise program; as this person progresses, the instructor would introduce a muscle power component (emphasising speed of execution). We will focus on exercises to be executed in the upright position, but exercises in a sitting position may be done to reduce the magnitude of the effort and/or to safety issues for some exercises.
4) Participants execute from 20 to 25 minutes of aerobic exercises. They perform bouts of walking (preferably ≥ 3 minutes/bout), intercalated by light exercises (using all large muscle groups, such as the muscles of the thigh, back and pectoral) disposed in a circuit-training format. These light exercises will avoid that, between two bouts of walking, participants' heart rate drops to the rest levels; it would warrant the maintenance of a sustained, moderate aerobic component.
5) Finally, the exercise session finishes with 5-minute calm down exercises (eg, very light walking followed by muscle stretching).

Social/recreational activity (control group)

The structured social/recreational intervention is an innovative approach introduced by the LEDEN study. The rationale for including an active comparator is to control for the additional positive effects of the exercise training on some outcomes (eg, neuropsychiatric symptoms) that would be related with the socialisation factor rather than promoted by the exercise itself. Participants in this group will participate in group-based activities (eg, painting), with no physical activity intervention or advices being provided to these participants. Interventionists will be professionals exterior to the NH. Although, for practical reasons, we did not define a single standard social activity intervention (the same intervention being not available in the geographical location of all participating NHs), the selected interventions must represent a new activity for the patient. A non-exhaustive list of potential social activities are: plastic arts (ie, practice of different art techniques, such as, painting, collage, modelling/shaping, etc.), musical mediation and musical instrument classes (ie, using

music and musical instruments to stimulate patients' communication and sensorial skills; practice of musical instruments), and singing classes and choir. It is important to highlight that such interventions will have the same schedule than the exercise intervention, ie, they will take place in the NHs, twice weekly, 60 minutes per session, during 6 months.

Outcome measures

Primary endpoint

*Functional ability***.** The effects of the 6-month interventions on the ability to perform ADLs will be evaluated using the Alzheimer Disease Cooperative Study (ADCS) ADL-sev.[33] This is a 19-item scale measuring the ability to perform basic (eg, bathing, toileting) and instrumental (eg, turning faucet/lights on/off) ADLs in the last four weeks. The ADCS-ADL-sev was specifically validated for people with moderate or severe Alzheimer's disease (AD), ie, the large majority of PWD in NHs. Scores in this scale vary from 0 to 54, with higher scores indicating better functional ability. The ADCS-ADL-sev has already been used successfully in the NH setting.[34]

Secondary endpoints

Overtime stability of ADL changes. We will investigate the 3- and 6-month postintervention stability of changes in functional ability (ADCS-ADL-sev).

Cost-effectiveness. The costs of implementing the interventions involve both initial fixed (ie start-up) costs of the exercise and social activity interventions as well as the costs of running the interventions' sessions. Start-up costs will be captured from the study budget: investment in exercise material, etc. The total costs of implementing the LEDEN intervention will be calculated from a societal perspective. Total costs will include: start-up costs, potential on-going costs (for instance: material renting, etc.), potential clinical costs (care that could be given after the physical sessions for patients experiencing pain), and intervention costs (salaries of interventionists). Note that our analyses will focus on the operating costs rather than the costs of research.

Therefore, economic analyses will be performed to explore whether the exercise program is cost-effective compared with the social activity program. The results of these analyses are useful from a health policy perspective as they will provide crucial information about the affordability of widespread implementation of the LEDEN interventions. Incremental cost-effectiveness ratio (ICER) calculations of the exercise training, compared to the social activity intervention, will be done. The primary effectiveness measure for the cost-effectiveness analysis will be the ADSC-ADL-sev measure. The ADCS-ADL-sev measured

among compliant patients compared with the social activity group will provide the incremental functional benefit resulting from the intervention at 3 months and at 6 months. To calculate the ICER, the additional cost attributable to the exercise compared with the social intervention will be divided by the differences in the ADCS-ADL-sev measures between the two groups: ICER (exercise session) = increase in cost due to exercise sessions / increase in the functional status. This ratio indicates the additional cost generated by the exercise program for increasing patients' ADCS-ADL-sev score of one unit. In addition, ICER for subgroups of NH residents will be computed. Heterogeneity in cost-effectiveness results among subgroups can indeed provide useful information for policy decision-maker in a context of limited available resources. Hence, ICER according to dementia severity and gender will be provided.

Furthermore, we will examine the effects of the 6-month interventions on:

Physical function. Physical function will be evaluated by the Short Physical Performance Battery (SPPB) (score from 0 to 12). The SPPB is a validated[35] performance battery composed of: timed short distance walk (4 meters at usual pace), timed repeated chair stands (5-repetition chair rise), and timed balance tests (standing balance). Each of these tests is assigned a score ranging from 0 to 4, with 4 indicating the highest level of performance and 0 the inability to complete the test. A summary score ranging from 0 (worst performers) to 12 (best performers) is calculated by adding walking speed, chair stands and balance scores.

Neuropsychiatric symptoms. The frequency and severity of neuropsychiatric symptoms will be assessed using the Neuropsychiatric Inventory – Nursing Home version (NPI-NH). The NPI is a validated[36] questionnaire investigating 10 behavioural and two neurovegetative areas; scores vary from 0 to 12 for each item, with higher scores indicating higher behavioural disturbances. The total NPI score is obtained by adding the scores of the 10 behavioural areas.

Pain. Pain will be evaluated by the Algoplus scale, which measures pain in older people unable to communicate verbally,[37] including PWD. This scale contains 5 items, each of them scored as 0 (absence of pain) or 1 (presence of pain); the total score varies therefore from 0 to 5, with higher scores indicating higher pain.

Nutritional status. This will be assessed using the Mini Nutritional Assessment (MNA), an instrument largely used in NHs.[38,39] Scores on the MNA vary from 0 to 30, with higher scores indicating better nutritional status.

Falls and fractures. The dates of falls and fractures (body region involved: wrist, hip, femur) will be recorded by the NH staff for each participant throughout the study. This information will be sent to the research team regularly.

Cognitive function. This will be assessed by the MMSE,[40] in its French version (French Health Authority (Haute Autorité de Santé - HAS) website: http://www.has-sante.fr/portail/plugins/ModuleXitiKLEE/types/FileDocument/doXiti.jsp?id=r_1497235 Accessed on June 15th 2015). Scores in this questionnaire vary from 0 to 30, with higher scores indicating higher cognitive function.

Time schedule

The overall duration of the study is two years. The interventions are preset to start between June and September 2015. Provisory calendar is: up to one year for setting up the study (from July 2014 to July 2015); one-to-two months for participants' recruitment (June/July 2015); six months for the intervention (from June/July 2015 to December/January 2016); six months for follow-up (from December/January 2016 to June/July 2016). Table 1 shows the calendar for the LEDEN study. Baseline assessments will occur only after obtaining the informed consent from patient's next of kin and legal representative, and from the patient him/herself if appropriate (according to understanding and communication skills). Table 2 shows patients' follow-up of data collection and outcome measures assessment.

Table 1. Calendar for the LEDEN study

Funding year	**2014 / 2015**				**2015 / 2016**			
Funding year - quarter	1 (Jul)	2 (Nov)	3 (Feb)	4 (May)	1 (Aug)	2 (Nov)	3 (Feb)	4 (May)
Activity								
Study setting up	X	X	X	X				
Participants' enrolment								
Eligibility screen				X				
Informed consent: patient, next of kin, and legal representative				X	X			
Randomisation/group allocation			X					
Baseline assessments				X	X			
Interventions				X	X	X	X	
Follow-up (post-intervention)						X	X	X
Close-out assessments								X
Data analyses						X	X	X

Table 2. Timeline for data collection and assessment of outcome measures.

Measurements	**Assessment timeline**					
	Eligibility screen	**Baseline (t0)**	**3-month intervention (t3)**	**Post-intervention (t6)**	**3-month post-intervention (t9)**	**6-month post-intervention (t12)**
Dementia	X					
Social/health-related variables		X				
Drugs		X		X		
ADCS-ADL-sev		X	X	X[a]	X	X
SPPB		X		X		
MMSE		X		X		
NPI-NH		X		X		
Algoplus		X		X		
MNA		X		X		

Note. ADCS-ADL-sev, Alzheimer Disease Cooperative Study-Activities of daily living-severe; MMSE, mini-mental state examination; MNA, mini-nutritional assessment; NPI-NH, neuropsychiatric inventory-nursing home; SPPB, short physical performance battery.

[a]The primary endpoint of this study is assessed using the ADCS-ADL-sev at t6, ie, at post-intervention.

Blinding

All assessments in the LEDEN study will be performed by the NH staff through a collaborative work of the NH coordinating physician with other NH staff members, particularly, nurses, nurses' aide, psychologists, and physiotherapists/ergo-therapists. Therefore, outcome assessors are the patient's healthcare providers and they will not be blinded to participants' group allocation. Blinding of patients is very difficult to make and maintain throughout the study in RCTs using behavioural interventions; in the LEDEN study, patients will not be blinded to group allocation. In an effort to reduce inter-rater assessment bias, the same assessors will evaluate participants throughout the study; however, this procedure will be dependent on staff turn-over. Moreover, the statistical analyst will be blinded to group allocation.

Sample size and recruitment

Because LEDEN is a pilot study designed to inform the development of a larger, multi-country controlled exercise trial among PWD living in NHs, feasibility is an important aspect to take into account. Thus, to facilitate the recruitment of NHs and the engagement of their staff in the success of LEDEN, we selected a convenience sample of for-profit NHs belonging to the Korian Group. The partnership with a private company in the healthcare and medico-social sector provided us with an easy access to a large number of NHs dealing with PWD patients, increasing the feasibility of LEDEN. Moreover, the fact that all NHs belong to the same private group may represent a methodological advantage for this small-size, pilot study since it may mean that the routine healthcare provided to patients are comparable across NHs (eg, similar ratios of coordinating physician, nurses, nurses' aide per bed, the use of the same protocols of care, etc). Although we are aware that such a procedure will reduce the generalisability of our findings, we made a clear methodological choice by privileging study feasibility instead of results generalisability.

To recruit NHs, the Korian group launched a call for volunteer participation in the LEDEN study across its NHs located in France; 37 NHs indicated to be interested in participating. After a thorough explanation about the LEDEN study and the practical implication of the NH staff in data collection through the whole duration of the study, only eight NHs remained interested in participating in LEDEN. All the eight NHs were therefore selected. Based on our previous experience in performing exercise RCTs in NHs,[41] we estimated that recruiting 140 PWD (ie, in average 18 PWD per NH) is feasible and will allow us to reasonably calculate accurate estimates of changes in our main outcome measure, ie, functional ability.

Randomisation

Due to organisation issues related to LEDEN interventions, the cluster randomisation had to be performed before patients' recruitment and baseline assessments. Indeed, LEDEN is a pilot study that partly relies on the NH staff engagement for its set up and implementation. NHs participating to LEDEN were geographically spread in the French territory (see Figure 1) and will have, thus, different interventionists; therefore, NH staff needs time to identify, contact, and recruit potential interventionists, particularly for the social activity intervention.

LEDEN is a cluster RCT with NHs as the unit of randomisation. Allocation ratio for exercise or control group is 1:1. Randomisation was performed by a statistician blinded to the identity of the NHs and not involved in the recruitment of facilities and patients or in data collection. The allocation sequence was stratified by the median value of the prevalence of dementia in the NH and was performed using random permuted block sizes of two within each of the two strata using the RALLOC command of Stata (StataCorp, College Station, TX). Sequentially numbered, opaque, sealed envelopes were used to warrant concealment of group allocation until the moment group assignment was revealed to participating NHs.

Figure 1. Geographical distribution of nursing homes participating in the LEDEN study. Map of France with the delimitations of the French Departments. Nursing homes participating in the LEDEN study are located in the areas highlighted with a dot: randomised nursing homes participating in LEDEN are represented by a black point, whereas the sole nursing home that withdrew from the study after randomisation is represented by a red point. This map was obtained from Pacha Cartographie at http://www.pacha-cartographie.com/fonds-de-carte/

Data collection and quality control

All data will be collected by the NH staff, except data related to the interventions that will be collected by the interventionists (for example, data on intervention compliance, participants' engagement in the intervention, or adverse events occurring during the intervention). The data will be collected in an electronic case report form. An internet-based, web browser application will be used to manage all the data regarding the assessment of the outcome measures. Entry into this area is password protected and encrypted; only the NH local coordinator (overall the NH coordinating physician) and his/her delegates (all of them NH staff members) have access to this area. NH local coordinators will have access only to the data regarding his/her own participants (ie, participants living in the NH where he/she is responsible for). Upon study completion, after all waves of data collection of the outcomes measures are finished and after the completion of the appropriate quality control procedures, the database is certified. The database is taken off-line and archived. The final datasets are then ready to be used; all data are stored in an anonymised format according to the current good clinical practice guidelines.

Most assessment tools are already used in clinical routine in NHs. Nevertheless, the staff of each participating NH received an in-person 2-hour training (provided by the researchers Yves Rolland and Philipe de Souto Barreto) on how to perform the assessments plus a 45-minute training (provided by the researcher Philipe de Souto Barreto) made by telephone on how to use the LEDEN website for data entry. Roughly, at least three staff members of each NH participated in the training sessions. Most of the time they were the NH coordinating physician, the referent nurse, and the psychologist, but also the NH director, physiotherapist, and ergo-therapist.

A clinical research associate appointed by the sponsor will regularly visit each study centre during the process of setting up the study, during the study depending on the frequency of inclusions, and at the end of the study. During these visits, the following aspects will be reviewed: informed consent; compliance with the study protocol and the procedures set out in it; and the quality of the data collected in the case report form: its accuracy, missing data, consistency of the data with the source documents (medical records, appointment diaries, etc.).

Statistical analysis

Data will be analysed using a modified intention-to-treat approach in which all participants with at least one postintervention assessment will be analysed. Multilevel analysis will be first performed separately on the primary outcome measure (ADCS-ADL-sev) using a three-level (with a random effect at the level of the NH and a random effect at the level of participants, ie, a model in which participants are nested within NHs) regression model

adjusted for the variable used to stratify the randomisation (ie, prevalence of PWD in the NH). Analysis for the secondary outcome measures will use similar three-level regression models. Statistical significance is determined by a $p < 0.05$. Secondary outcomes will be adjusted for multiple comparisons using the False Discovery Rate,[42] ie, the proportion of true null hypotheses rejected among the rejected. For example, in the Hochberg procedure,[42] we order the observed p-values from largest to smallest; if the largest observed p-value is < 0.05, then all the tests performed are significant. If not, we compare the second largest observed p-value to the next threshold of 0.05/2, ie, 0.025, and so on. Analyses will be performed using Stata (v.14.0, Texas, USA) and SAS (v. 9.3, SAS Institute Inc, Cary, NC) statistical software.

Ethics

The LEDEN study follows the principles of the Declaration of Helsinki and complies with ethics standards for research in France. The NH coordinating physician firstly obtained the signed informed consent from the next of kin and the legal representative (if appropriate) of all potentially eligible participants. Then, a member of NH medical staff informed all potentially eligible participants about the study and its objectives, and tried to collect a signed consent as appropriate (due to the very low cognitive function and communication skills of PWD in NHs, we expected that the majority of potentially eligible participants would be unable to provide a signed informed consent). Next of kin, legal representatives, and patients were informed verbally and by written that study participants may withdraw from the study at any time during the study.

The study protocol has already been approved by the Advisory Committee for the Protection of Persons participating in Biomedical Research (CPP SOOM III. Registration number: 2014-A01713-44), the Consultant Committee for the Treatment of Information in Research on Health (CCTIRS. Registration number: 15.159) and the National Agency for the Security of Drugs and Health products (ANSM. Registration number: 141502B-31). The LEDEN protocol was registered in a clinical trial registry under the following identifier: NCT02444078.

Discussion

The most innovative aspect of LEDEN is the operationalisation of a well-structured socially-active control group. Since developing an exercise intervention in PWD who live in NHs is more difficult to organise and comprises more health risks than doing other social/recreational activities, it is indispensable to know whether the health benefits associated

with exercise outweigh its risks in this vulnerable population and whether the exercise intervention is viable in terms of cost-effectiveness.

Most RCTs of exercise for institutionalised PWD performed to date have had a short length. According to a recent review,[24] only two studies had an intervention length of 6 months or over, and only one (a RCT performed by our team[41]) was rated as having a high-quality design. Short-term interventions may constitute a shortcoming because very old, institutionalised PWD with moderate to severe dementia probably needs more time to adapt to and to progress on exercise, compared with healthier older adults. Although one could argue that exercise may be associated to health risks, such as cardiovascular events, falls and fractures, the most recent and updated Cochrane review and meta-analysis about exercise for PWD stated that none of the reviewed studies reported serious adverse events attributable to the exercise intervention.[11] Moreover, although the exercise training in the LEDEN study will be designed to be challenging for participants, it will be led by professional exercise instructors with experience in exercise for PWD as well as exercise in the NH setting.

The importance of exercise for health promotion has already been demonstrated in different populations. Regarding PWD living in NHs, LEDEN will provide the preliminary evidence needed to inform the development of larger and more complex (eg, involving several countries with different health systems) interventions using exercise or non-exercise social interventions.

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Main Results[2]

Functional ability, cognitive function, and physical performance

Introduction

People with dementia (PWD) living in nursing homes (NH) are characterised by high levels of disability, multimorbidity, and polypharmacy[1] (in particular antipsychotic drugs).[2,3] The number of older adults living in NHs is expected to increase in the coming decades[4] and dementia is very prevalent in this setting[5] and is a risk factor for disability.[6] Therefore, non-pharmacologic interventions aiming to slow down the progression of the disabling cascade among PWD in NHs represents a public health priority.

Exercise, a subset of physical activity that is structured, repetitive and purposeful, is a powerful intervention to improve or maintain functional status in the institutionalised elderly.[7,8] Although exercise may improve dementia care by addressing other health issues (eg, depression, sarcopenia),[9,10] evidence on the benefits of exercise on the functional status of PWD is inconsistent.[11] Randomised controlled trials (RCT) of exercise for institutionalised PWD performed to date had a few methodological limitations, such as, lack of cluster randomisation (to avoid contamination among study arms) or short intervention length (less than 16 weeks for most of them). Furthermore, the control comparator group was, in most cases, composed of usual care or social unstructured activities (eg, casual conversations). Although structured activities specifically designed for PWD have the potential to improve health outcomes, they were rarely operationalised as an active comparator group.

The purpose of this study was to examine the effects of a 24-week pilot cluster-RCT of group-based exercise, compared to well-structured group-based social activities, on the ability to perform activities of daily living (ADL) among PWD living in NHs (LEDEN study). We hypothesised that exercise, compared to social activities, would slow down the progression of functional loss.

Methods

The methods and procedures of LEDEN were published in details elsewhere[12] and will be briefly described hereafter. The study protocol has been approved by the Ethics Committee (CPP SOOM III) and was registered in a clinical trial registry (registration number:

[2] One paper on this data was already submitted for publication and is currently under review in a high-impact scientific journal.

NCT02444078). Patients (if applicable), next of kin, and legal representative signed an informed consent form, as appropriate, before baseline assessments.

Participants

Participants were enrolled in the study between August and October 2015. The medical staff of the French NHs that volunteered to participate in LEDEN screened their patients for eligibility: *Inclusion criteria*. diagnosis of Alzheimer's disease, vascular or mixed dementia according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); mini-mental state examination (MMSE) ≤ 20/30; age ≥ 65 years-old; living in the NH for at least one month (instead of three months; amendment added to the protocol and approved by the ethics committee); ability to walk 4 meters (no human assistance); ability to rise from a chair (minimal human assistance allowed). *Exclusion criteria.* terminal illness with life expectancy less than six months; diagnosis of Parkinson's disease or dementia with Lewy bodies; unstable condition precluding participation in exercise training; planned transfer from the NH during intervention period; participation in another exercise program ≥2 times/week in the last 2 months. Sample selection bias was avoided by inviting to participate in the study all NH residents meeting the above mentioned criteria.

Randomisation and masking

LEDEN is a two-arm pilot cluster-RCT, with NHs as the unit of randomisation. NHs were randomised to a 24-week intervention in either the exercise group (EG) or the social group (SG) following a 1:1 ratio. Randomisation was performed by a statistician blinded to the NHs identity and not involved in any other aspect of LEDEN. Group allocation was stratified by the median value of dementia prevalence in NHs and was performed using random permuted block sizes of two within each of the two strata. Group allocation concealment was guaranteed by the use of opaque, sealed envelopes until the moment group assignment was revealed to the NHs.

Study design and procedures

LEDEN is a pragmatic pilot study. Intervention length was six months. Due to its pragmatic design, feasibility was an important aspect of LEDEN and, thus, the study partly relies on the direct participation of NH staff. Randomisation occurred before baseline assessments to avoid a too large time interval between participants' assessment and the beginning of the interventions. In fact, the NH staff was responsible for identifying and selecting interventionists, particularly for SG. All outcome measures as well as data on adverse health events were assessed and recorded by the NH staff (unblinded to group

assignment) via a devoted password-protected online platform; after post-intervention outcome assessments and the required data quality control, dataset was certified and the access to modify information regarding the 6-month intervention period was locked. The research team conducted in-person trainings to NH staff on all study procedures.

Interventions

Exercise

Exercise instructors had a 3-year university diploma in physical activity. They had experience in working with institutionalised PWD. Exercise sessions were group-based and the exercise programme was individualised to enhance its potential efficacy and improve adherence. The interventiojn took place in the NH, twice/week, during 60 minutes/session, for 24 weeks. The exercise intervention was a multicomponent training: 10 minutes of warm-up (eg, range-of-motion, light walks), 10 minutes of coordination/balance exercises (eg, short walks with direction changes), 10-15 minutes of muscle strengthening (weight-bearing and hand-held materials), 20 minutes of aerobic exercises (mostly bouts of walks), and 5-10 minutes of cooling-down. Exercise intensity was targeted to be moderate and progression was established individually, according with participants' physical capabilities. Visual cues were used by instructors for reaching the targeted intensity; participants were regularly stimulated to improve their performance in the absence of pain or breathlessness.

Social activity group (SG)

Interventionists for the SG were professionals with experience in working with institutionalised PWD. Patients in SG participated in group-based activities that took place in the NHs, twice/week, during 60 minutes/session, for 24 weeks. The selected interventions represented a completely new activity for the patient. No exercise intervention or specific advices for increasing physical activity levels have been provided to these participants. For practical reasons, no predefined model of social activity was established because the same intervention could not always be feasible/available across the participating NHs. NHs randomised to SG received one of the following interventions: therapeutic musical mediation (one NH; eg, relaxation with music, playing percussion instruments, singing, and light dancing) or plastic arts (two NHs; eg, painting and drawing alone and in duo, clay modelling).

Outcomes

The pre-specified, main outcome measure of LEDEN was patients' functional status, as measured by the Alzheimer's Disease Cooperative Study-ADL-severe (ADCS-ADL-sev) scale,[13] an assessment tool specifically validated for people with moderate or severe dementia.

This is a 19-item scale (range 0-54, with higher scores indicating better function) measuring the ability to perform basic (6 items, eg, bathing, toileting) and instrumental ADL (IADL, 13 items, eg, turning faucet/lights on/off) in the last four weeks. Participants' ADL function was assessed thrice during the 6-month intervention period: baseline, three- and six-month.

The pre-specified secondary outcomes were assessed twice (baseline and 6-month) and were: 4-meter usual gait speed (m/sec), cognitive function as measured by the MMSE (scores varying from 0 to 30; higher is better),[14] lower-limb function as measured by the short physical performance battery (SPPB,[15] a validated tool composed of three timed subtasks (usual gait speed, chair stand, and balance tests), scores ranging from 0 (worst performers) to 12 (best performers)), neuropsychiatric symptoms (neuropsychiatric inventory,[16] scores ranging from 0 to 120, higher is worse), pain (Algoplus scale,[17] scores ranging from 0 to 5, higher is worse), nutritional status (mini-nutritional assessment,[18] scores ranging from 0 to 30, higher is better). In this article we examined the effects of the interventions on functional-related outcomes: ADCS-ADL-sev, gait speed, SPPB, and MMSE.

Adverse events

Mortality, fractures, emergency department (ED) visits, non-scheduled hospitalisations (hospital stay of 24h or longer), non-injurious and injurious falls[19] were recorded throughout the 6-month intervention period.

Statistical analysis

Since LEDEN is a pilot study, no formal sample size calculation was performed. Descriptive statistics are presented as means (SD) or median (interquartile range – IQR) and percentage, as appropriate. Baseline differences between groups, as well as differences on adverse events and dropouts, were checked using chi-squared test or the Fisher's exact test, and Student t-test or the Wilcoxon rank sum test, as appropriate. Intra-cluster correlation (ICC) for baseline, 3- and 6-month were obtained using ANOVA. Efficacy analyses were performed, as pre-specified in the protocol, using a modified intention-to-treat (ITTmod) approach including all participants with at least one post-baseline assessment for the ADCS-ADL-sev. Multilevel analysis were performed on ADCS-ADL-sev using a three-level (with random effects at the levels of both NHs and participants (ie, participants nested within NHs) and a random slope on time) regression model with group, time, and group-by-time interaction as fixed effects. Models were adjusted (fixed-effect) for the variable used to stratify the randomisation (ie, prevalence of dementia in the NH) and for potential

confounders that differed between groups at baseline. Analysis on MMSE, gait speed and SPPB scores used similar three-level regression models. Adjusted means for each group were obtained from the models and adjusted mean differences were calculated. Statistical significance was determined by a $p < 0.05$. In case of statistical significance across secondary outcomes, multiplicity was taken into account using the False Discovery Rate.[20] Analyses were performed with Stata (v.14.0, Texas, USA) statistical software.

Sensitivity Analysis

Post hoc, exploratory sensitivity analyses on ADCS-ADL-sev were performed by: (1) adding intervention adherence (continuous, in %) to the mixed-effect regression; (2) restricting the model to people with at least 50% adherence (removing people that participated less than once/week in interventions); (3) removing from the model "fast decliners" defined as people having declined on the ADCS-ADL-sev of two SD or more between baseline and post-intervention. Fast decliners may drive associations through a phenomenon known as the "horse-racing effect" (ie, bias related to a potential lack of overtime stability of an outcome, since individual trajectories for that outcome during a timeframe before inclusion of the participant in a RCT is unknown);[21] (4) performing analysis separately for basic ADLs and IADLs.

Results

Figure 1 displays the flowchart of the study. Eight NHs volunteered to participate and were randomised, four NHs per study group; one NH in SG withdrew before participants' recruitment phase. Ninety-eight patients across the seven participating NHs met eligibility criteria and volunteered to participate, but one person in the EG died before baseline assessments. Therefore, 97 patients from seven NHs were recruited (cluster sizes were: 8, 9, 12, 13, 17, 18, and 20); among them, six residents (three in each group) had no follow-up assessment for the primary outcome, and were consequently removed from efficacy analyses. The six dropouts did not differ ($p > 0.05$) from the remaining 91 participants included in analyses for socio-demographic (ie, age, sex and education) and health-related variables (including the ADCS-ADL-sev). The number and reasons for dropping out did not differ between groups.

Figure 1. Flowchart of nursing homes and subjects in the study

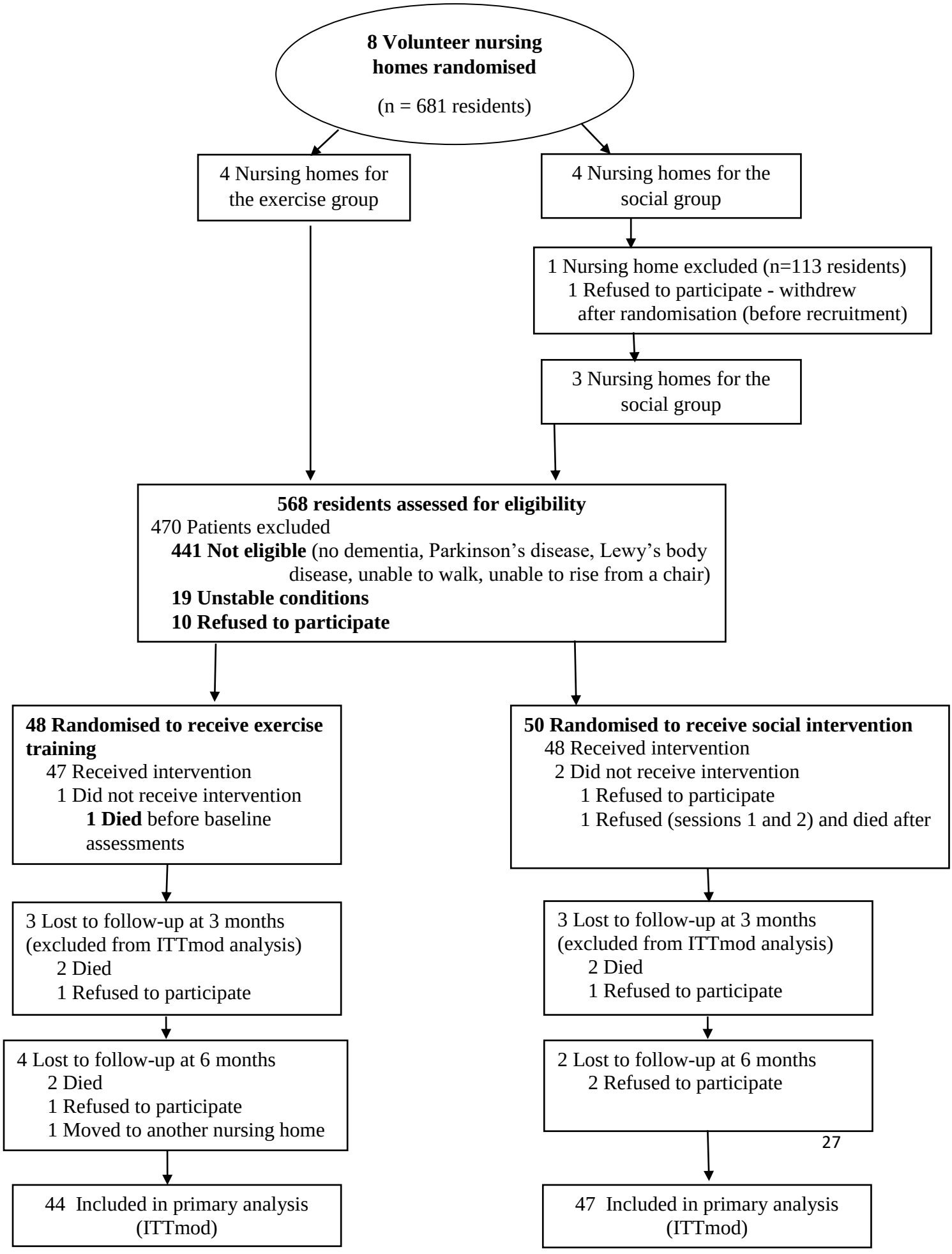


Table 1 shows baseline characteristics of the 91 participants included in analyses. Groups were similar for most variables, but differed for sex distribution, neuropsychiatric symptoms, and nutritional status.

Table 1. Baseline characteristics and differences between groups.*

Variables	Exercise (n=44)	Social activity (n=47)	p-value
Age (years)	88.3 (5.1)	86.9 (5.8)	0.23
Sex			0.03
Women	41 (93.2)	36 (76.6)	
Men	3 (6.8)	11 (23.4)	
Education			0.48
No diploma	11 (25)	11 (23.4)	
Secondary education (no high-school diploma)	27 (61.4)	25 (53.2)	
High-school diploma or higher	6 (13.6)	11 (23.4)	
Number of diseases†‡	1.5 (1 – 2)	2 (0 – 3)	0.81
BMI (kg/m²)†	23.5 (20.4 – 27.4)	22.9 (21.4 – 25.8)	0.80
MNA (0 to 30 score)†	22 (19.7 - 23.7)	21.5 (18.5 - 22.5)	0.03
NPI 10-item (0 to 120 score)†	18.5 (10.5 - 39)	14 (4 - 21)	0.03
Pain (Algoplus: 0 to 5 score)†	0 (0 – 1)	0 (0 – 1)	0.33
ADCS-ADL-sev (0 to 54 score)	21 (11)	20.3 (10.3)	0.75
MMSE (0 to 30 score)	11.4 (6.2)	10.8 (5.5)	0.60
SPPB (0 to 12 score)	4.4 (2.4)	4.5 (2.3)	0.74
Usual gait speed (m/sec)	0.48 (0.23)	0.48 (0.18)	0.97

Note. ADCS-ADL-sev, Alzheimer's Disease Co-operative Study - Activities of Daily Living - severe; BMI, body mass index; MMSE, mini-mental state examination; MNA, mini-nutritional assessment; NPI, neuropsychiatric inventory; SPPB, short physical performance battery.

*Values are means (SD) for continuous and ordinal variables and absolute numbers (%) for categorical variables, unless otherwise stated.

†Values are median (interquartile range)

‡Dementia was not included in the calculation of the number of diseases

A total of 48 hours of exercise or social activities were provided; due to internal organisational issues, one NH in SG provided the 48hr of intervention spread in 34 sessions. Median (IQR) adherence was 74% (42% - 88%) in EG and 83% (50% - 91%) in SG (p = 0.41). ICC for all outcomes and time-points are presented in Table 2.

Table 2. Intra-cluster correlation coefficients.

Outcome measures	**ICC at baseline**			**ICC at 3-month (intervention)**			**ICC at 6-month (post-intervention)**		
	Whole sample (n=97)	Exercise group (n=47)	Social group (n=50)	Whole sample (n=91)	Exercise group (n=44)	Social group (n=47)	Whole sample (n=85)	Exercise group (n=40)	Social group (n=45)
ADCS-ADL-sev	0.08	0.09	0.08	0.14	0.05	0.16	0.14	0.18	0.10
MMSE	0.08	0.11	0.03	-	-	-	0.11	0.10	0.12
SPPB	0.11	0.14	0.06	-	-	-	0.06	0.07	0.04
Usual gait speed*	0.21	0.29	0.09	-	-	-	0.06	0.09	0.02

Note. ADCS-ADL-sev, Alzheimer's Disease Co-operative Study - Activities of Daily Living - severe; ICC, intra-cluster correlation coefficient; MMSE, mini-mental state examination; SPPB, short physical performance battery

*Sample size for gait speed was smaller than for the other outcomes due to inability in walking four meters: 43 and 49 people at baseline, and 33 and 38 at 6-month for the exercise group and the social group, respectively.

Results of multilevel models adjusted for the prevalence of dementia in NHs, sex, neuropsychiatric symptoms and nutritional status are shown in Table 3 and Figure 2. Group-by-time interaction was not significantly associated with any of the studied outcomes, indicating that the effects of exercise did not differ from the effects of social activities. Between-group adjusted mean differences over six months indicated that EG declined more than SG on the ADSC-ADL-sev (95% CI: -5.1 to 1.2) and MMSE (95% CI: -1.9 to 0.8), whereas SG declined more than EG on usual gait speed (95% CI: -0.04 to 0.14) and SPPB (95% CI: -0.4 to 1.6), but none of those differences were statistically significant.

Table 3. Effects of the LEDEN interventions on functional ability, cognition, and physical function outcomes.

Outcomes	**Exercise group**		**Social control group**		**Between group adjusted mean difference (95% CI)†**	**p-value**	**β-coefficient for time-by-treatment interaction (95% CI)‡**	**p-value**
	n*	**Within group adjusted mean difference (SE)**	**n***	**Within group adjusted mean difference (SE)**				
ADCS-ADL-sev: *3-month*	44	-3.1 (0.98)	47	1.8 (0.95)	-4.9 (-7.6 to -2.3)	< 0.001	-0.35 (-0.87 to 0.17)	0.19
6-month		-3.9 (1.2)		-2.0 (1.1)	-1.9 (-5.1 to 1.2)	0.23		
MMSE	44	-1.0 (0.51)	47	-0.5 (0.47)	-0.55 (-1.9 to 0.8)	0.43	-0.09 (-0.32 to 0.14)	0.43
SPPB	44	-0.2 (0.36)	47	-0.8 (0.34)	0.6 (-0.4 to 1.6)	0.22	0.10 (-0.06 to 0.26)	0.22
Usual gait speed	43	0.07 (0.03)	46	0.03 (0.03)	0.05 (-0.04 to 0.14)	0.30	0.01 (-0.01 to 0.02)	0.30

Note. ADCS-ADL-sev, Alzheimer's Disease Co-operative Study - Activities of Daily Living - severe; CI, confidence interval; MMSE, mini-mental state examination; SE, standard error; SPPB, short physical performance battery.

*Number of participants entered into the regression models.

†Negative values indicates higher declines in the exercise group, compared to the social group, while positive values indicates higher declines in the social group, compared to exercisers.

‡The social control group is the reference category.

Figure 2. Effects of exercise and social activity on functional status, cognitive function, and performance-based tests of physical function.

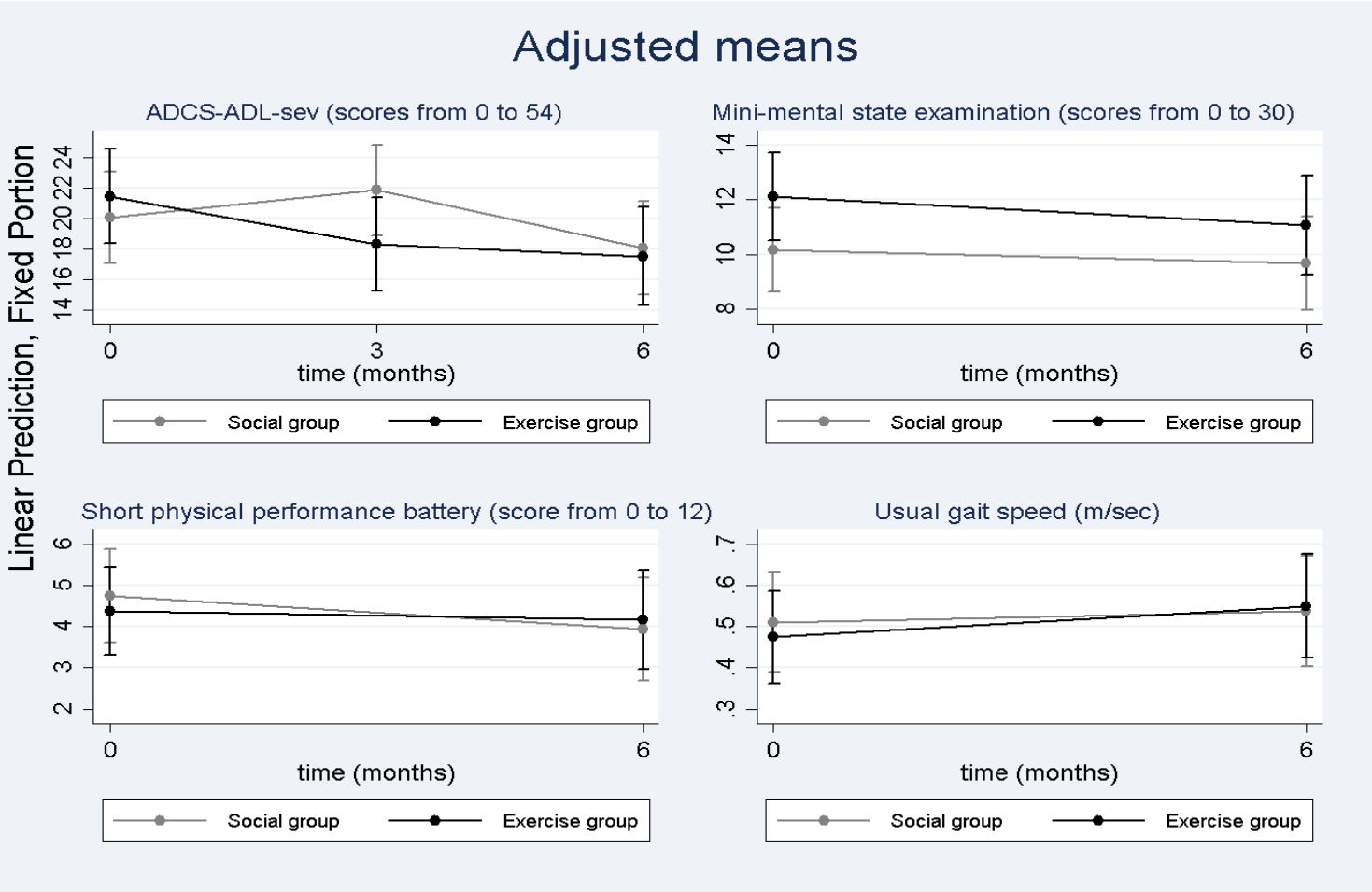
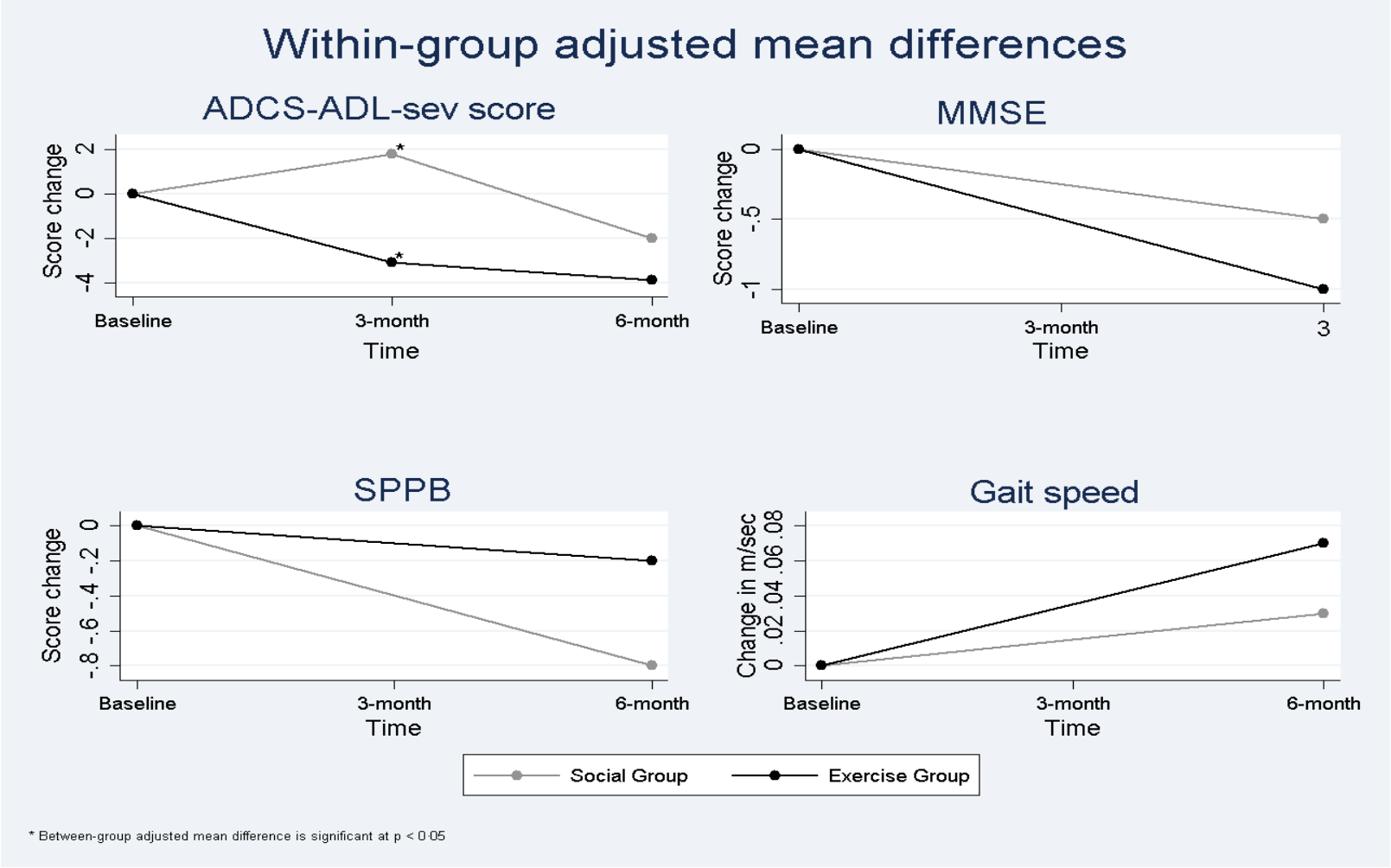


Figure 3 shows the score change between baseline and post-intervention (six months) for all outcomes.

Figure 3. Score change of clinical outcomes over the 6-month intervention period



All sensitivity analyses on the global ADCS-ADL-sev score provided unchanged results as showed in Table 4.

Table 4. Sensitivity analyses of the effects of the LEDEN interventions on functional ability (ADCS-ADL-sev scale).

Sensitivity analysis	**Exercise group**		**Social control group**		**Between group adjusted mean difference (95% CI)†**	**p-value**	**β-coefficient for time-by-treatment interaction (95% CI)‡**	**p-value**
	n*	**Within group adjusted mean difference (SE)**	**n***	**Within group adjusted mean difference (SE)**				
Sensitivity analysis 1: adding adherence rates								
3-month	44	-3.1 (1.0)	47	1.8 (0.9)	-4.9 (-7.6 to -2.3)	< 0.001	-0.35 (-0.87 to 0.17)	0.18
6-month		-3.9 (1.1)		-2.0 (1.1)	-1.9 (-5.1 to 1.2)	0.22		
Sensitivity analysis 2: restricted to people with ≥ 50% adherence								
3-month	31	-2.2 (1.1)	36	1.7 (1.0)	-3.9 (-6.9 to -0.8)	0.012	-0.31 (-0.88 to 0.26)	0.28
6-month		-3.2 (1.3)		-1.3 (1.2)	-1.9 (-5.3 to 1.6)	0.29		
Sensitivity analysis 3: removing fast decliners								
3-month	39	-2.1 (0.9)	46	1.6 (0.8)	-3.7 (-6.0 to -1.3)	0.003	0.02 (-0.41 to 0.45)	0.92
6-month		-1.3 (0.9)		-1.6 (0.8)	0.3 (-2.2 to 2.7)	0.84		
Sensitivity analysis 4: separated analysis for basic ADLs (six items) and IADLs (13 items)								
Basic ADL: *3-month*	44	-0.6 (0.4)	47	0.3 (0.4)	-0.9 (-2.0 to 0.2)	0.10	-0.09 (-0.33 to 0.14)	0.44
6-month		-1.7 (0.5)		-1.1 (0.5)	-0.5 (-1.9 to 0.9)	0.46		
IADL: 3-*month*		-2.3 (0.7)		1.5 (0.7)	-3.9 (-5.7 to -2.0)	< 0.001	-0.40 (-0.75 to -0.05)	0.025
6-month		-2.6 (0.8)		-0.3 (0.7)	-2.3 (-4.4 to -0.2)	0.032		

Note. ADCS-ADL-sev, Alzheimer's Disease Co-operative Study - Activities of Daily Living - severe; CI, confidence interval; SE, standard error.

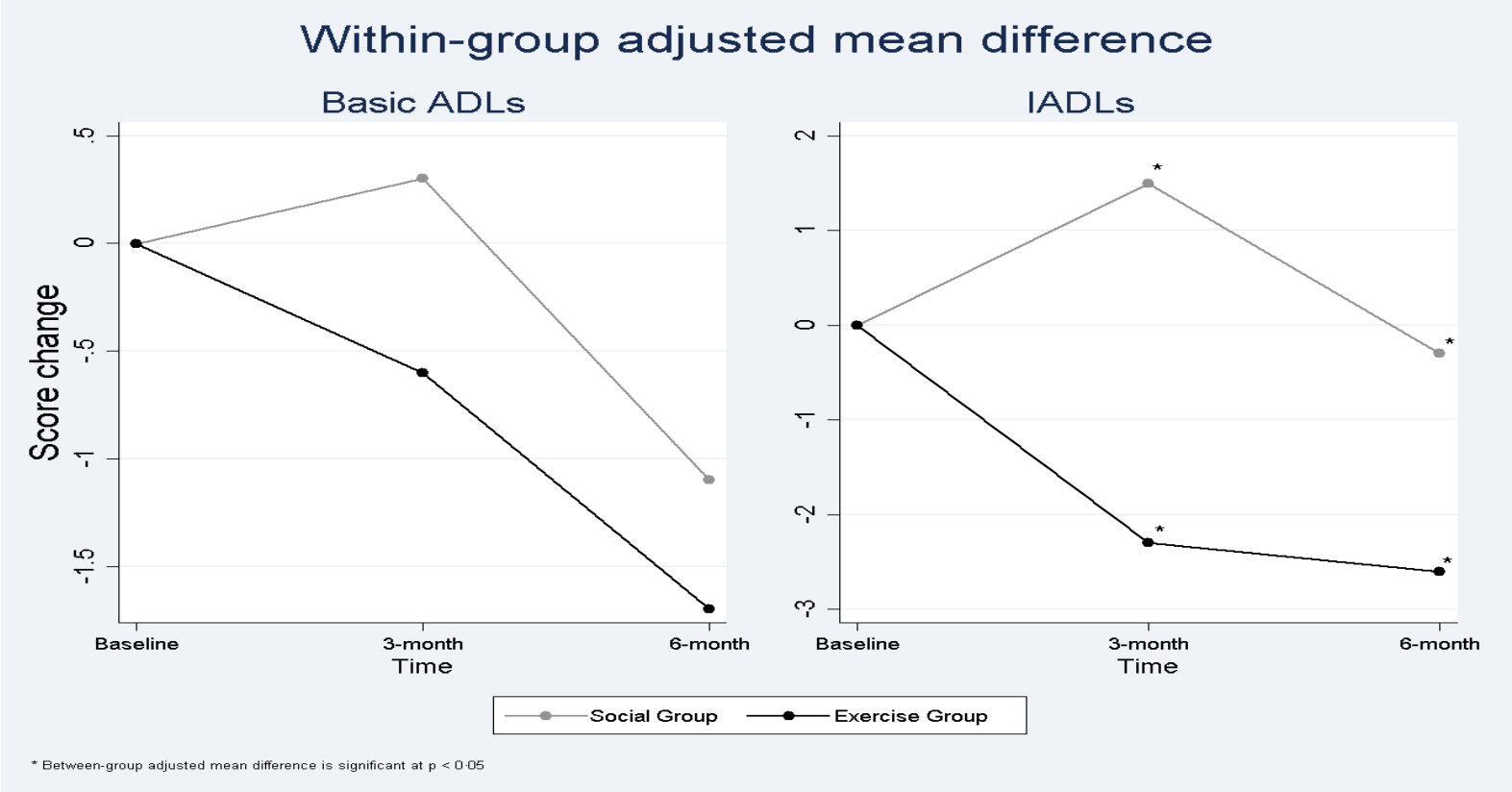
*Number of participants entered into the regression models.

†Negative values indicates higher declines in the exercise group, compared to the social group, while positive values indicates higher declines in the social group, compared to exercisers.

‡The social control group is the reference category.

Figure 4 displays the results of separated analyses for basic ADLs and IADLs subscales. Analysis restricted to the 6-item basic ADL subscale found similar null results. However, analysis on the 13-item IADL showed that the group-by-time interaction was significantly associated to that outcome, favouring SG (B-coefficient -0.40, 95% CI -0.75 to -0.05; p= 0.025); between-group adjusted mean differences showed that EG declined more than SG at 3-month (-3.9; p < 0.001) and 6-month (-2.3; p = 0.03) follow-ups.

Figure 4. Basic ADL and IADL score change over the 6-month intervention period



Power analysis and sample size calculations (SAMPSI command in Stata) using the SD and intra-class correlation coefficients observed in our study found we had a 53% power to detect a significant effect if the true difference was the observed 1.9 point difference between groups in the adjusted-change score of the ADCS-ADL-sev at six months; to detect this difference with 90% power, a sample size of 228 subjects (n=114 per study arm) would be needed.

Adverse events

Adverse events during the 6-month intervention showed no difference between groups for death, fractures, ED visits, and hospitalisation (Table 5). The number of falls (p = 0.04) and the number of participants falling (p = 0.04) were significantly higher in SG compared to EG. No differences were found in terms of injurious falls.

Table 5. Adverse events per study group during the 6-month intervention period.

Adverse event	**Number of people (%)**			**Number of events**		
	Exercise group n = 47	Social activity n = 50	p-value	Exercise group n = 47	Social activity n = 50	p-value
Death	4 (8.5)	2 (4)	0.43	4 (8.5)	2 (4)	0.43
Fractures	2 (4.3)	3 (6)	0.70	2	3	0.70
ED visits	6 (12.8)	3 (6)	0.31	8	3	0.24
Hospitalisation (≥24h)	6 (12.8)	2 (4)	0.15	7	2	0.11
Falls	8 (17)	18 (36)	0.04	25	36	0.04
Injurious falls	5 (10.6)	8 (16)	0.55	10	8	0.34

Note. ED, emergency department.

Discussion

This cluster-RCT found no differences in the effects of an exercise intervention compared with a social intervention on ADL performance, and physical and cognitive function in PWD living in NHs. Study groups had similar adherence rates to the interventions and did not differ in adverse health events, except that SG fell more than EG.

Our team[22] and others[23,24] have proven that exercise, compared to usual care, had positive effects on ADL performance among institutionalised PWD. However, the results

have been mixed for trials comparing exercise to structured social activities in this population. Similar to our findings, other two RCTs[25,26] among institutionalised PWD, in which participants were slightly younger and with higher cognitive function than those in our study, have found no differences on ADL performance between exercisers and controls who have received structured, social activities. Telenius et al.[26] also found no post-intervention difference between groups on gait speed. Those RCTs had a 3-month[26] and 4-month[25] intervention length, which is inferior to the ours. Another RCT[27] of exercise versus structured social activities in NH residents showed no difference between groups on ADL performance at the end of the 3-month intervention; however, subgroup analysis restricted to PWD (n=95 in the analysis) found a positive effect of exercise on ADL performance, compared to controls. Therefore, the LEDEN study adds information to the sparse literature showing that a medium-term (six months) cluster-RCT of an exercise intervention against structured social activities for institutionalised PWD has had no effects on functional status, and motor and cognitive function.

Although not statistically significant, post-intervention between-group adjusted mean differences can be considered as clinically meaningful for the ADCS-ADL-sev[28] (1.9 points favouring the social control group), SPPB, and gait speed[29] (0.6 points and 0.05 m/sec, respectively, favouring the exercise group). Since EG declined less on physical performance, but more on ADL function, we may hypothesise that the social activities proposed to SG slowed down declines on ADL through a mechanism independent of motor skills; for example, by delaying the decline on tasks requiring more cognitive than motor efforts. Although we have no data on specific cognitive functions (eg, executive function, attention) to examine a potential effect of the social intervention on these outcomes, the results of the exploratory analysis restricted to the IADL subscale of the ADCS-ADL-sev, which is composed of tasks that require cognitive effort (eg, using the phone, participating in conversation), points in this direction since EG declined more on IADLs than SG. The hypothesis that structured social activities would positively impact ADL performance through improved cognitive function or through another unknown mechanism (such as enhanced motivation) requires further investigation.

This study has multiple positive points that are important to highlight: our findings will inform a larger, well-dimensioned and definitive cluster RCT, not only in terms of sample size calculations but also regarding design-related issues, such as the assessment of selected outcomes (particularly study primary endpoint) before baseline assessments in order

to examine outcome stability on an individual basis; intervention length was longer than most RCTs of exercise for institutionalised PWD; exercise regimen in LEDEN followed several aspects of the recent evidence-based guidelines of exercise for NH residents:[10] multicomponent training focusing on aerobic exercises and strength training, moderate-intensity, frequency of twice/week, and session duration of 60 minutes. Several limitations are, however, worth mentioning: first, it was a pilot study, with a small sample size. Based on our previous experience of exercise RCT among institutionalised PWD,[22] we expected to be able to recruit 140 participants, which proved to be an over-expectation. Sample size calculations using data from LEDEN showed that a study with 114 subjects per group would provide 90% power to detect a 1.9-point difference between groups on the ADCS-ADL-sev. Secondly, due to its pragmatic design and budget limitations, NH staff were the outcome assessors and, therefore, they were unblinded to group assignment. However, this bias was unlikely to having impacted our findings since it was present in all participating NHs; thirdly, LEDEN involved only private for-profit NHs belonging to the same company. Although it means that patients received a standard care across NHs, we are conscious this reduces the generalizability of our findings.

In sum, we found that the effects of a 6-month exercise intervention for PWD living in NHs did not differ from those of a well-structured social activity on ADL performance, physical and cognitive function. A larger and longer cluster-RCT is needed to definitively establish if exercise training, compared to a non-physical intervention, has any additional health benefit to institutionalised PWD. Such an information has important practical and public health implications since, compared to exercise, non-physical activities are easier to organise in NHs, lead to higher adherence, exposes residents to less physical risks, and can be executed in larger groups at a time, which may represent reduction in costs.

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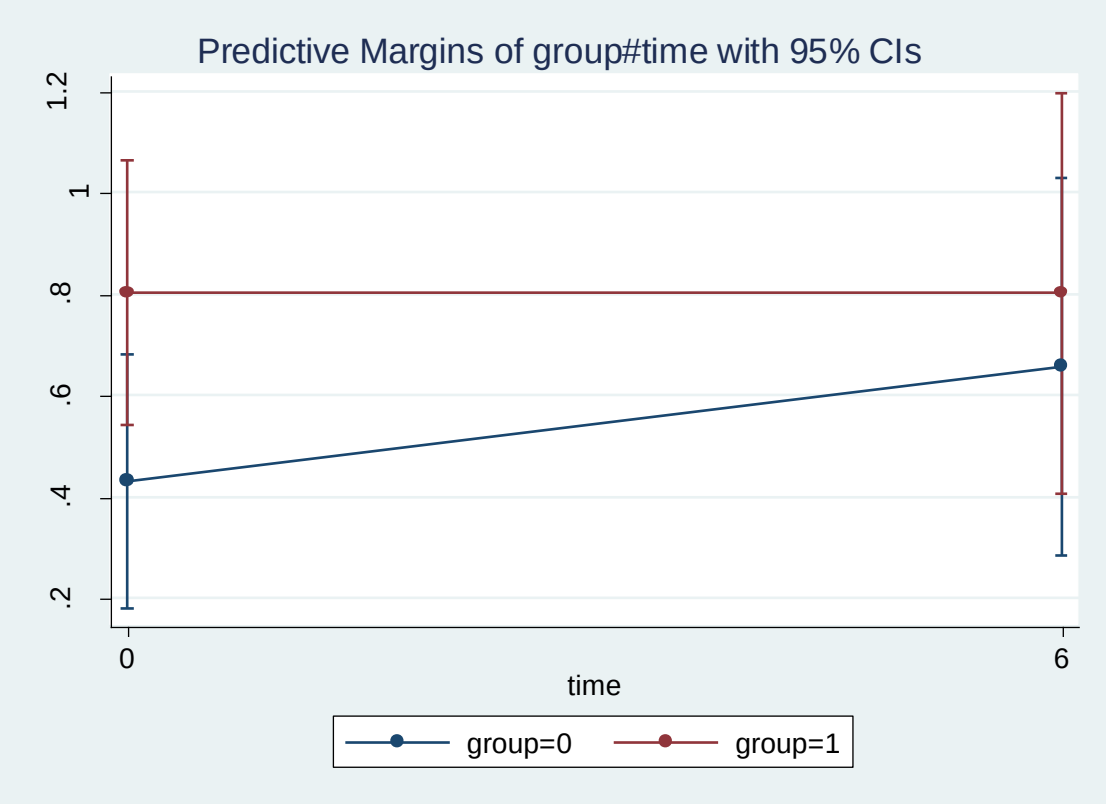
Preliminary Results[3]

Pain, Neuropsychiatric symptoms, and Nutritional status

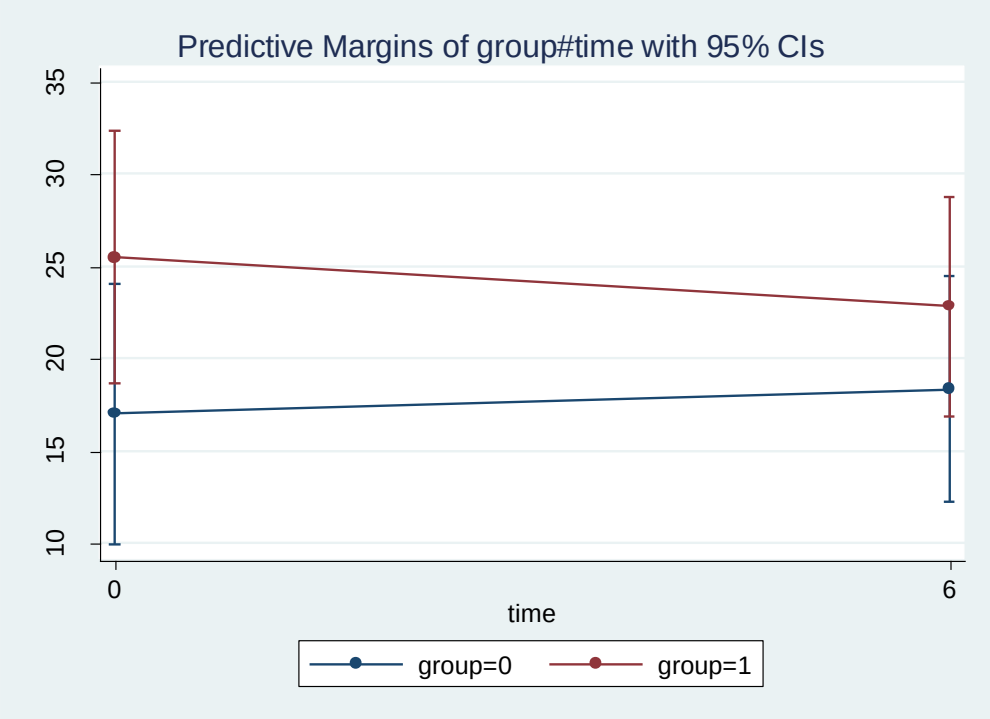
Note. For all three graphs presented below, group=0 represents social activity intervention, whereas group=1 corresponds to the exercise intervention. Roughly, the results of multilevel models adjusted for the prevalence of dementia in NHs, sex, neuropsychiatric symptoms and nutritional status found that group-by-time interaction was not significantly associated with any of pain, neuropsychiatric symptoms (both NPI 10-item and 12-item), and nutritional status, indicating that the effects of exercise did not differ from the effects of social activities. Although nutritional status was improved in the social activity group compared to the exercise group ($p < 0.05$ for between-group adjusted mean differences), this association was no longer statistically significant after adjustment for multiplicity as pre-planned in the study protocol.

Pain (Algoplus)

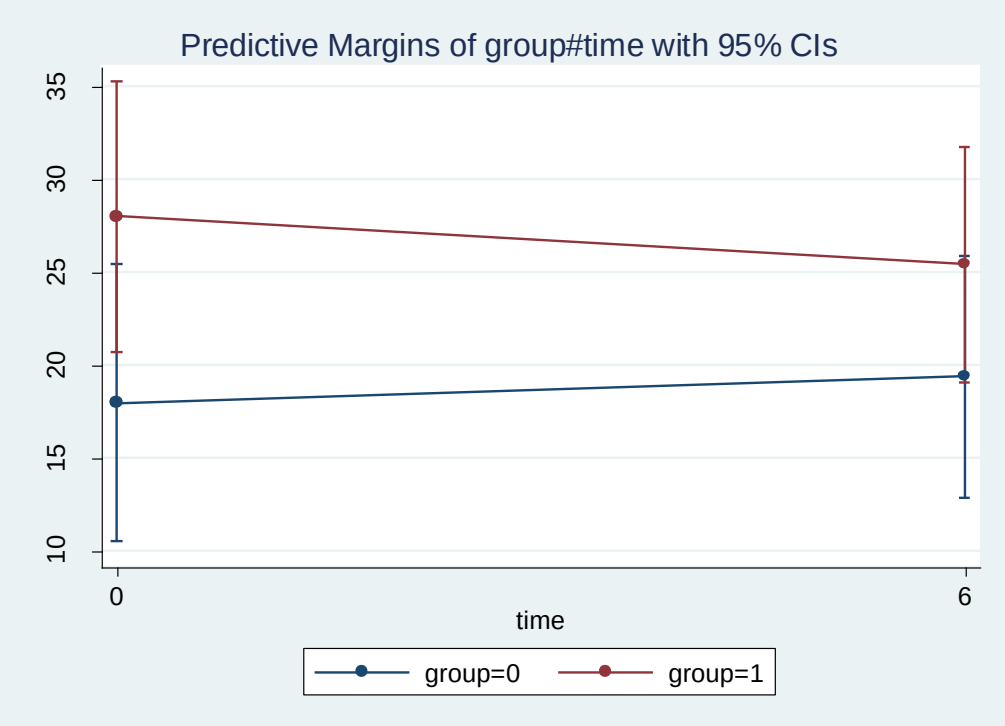


[3] One paper is currently under redaction on this data and will be nearly submitted for publication in a high-impact scientific journal.

Neuropsychiatric symptoms (Neuropsychiatric Inventory **10-item, score from 0 to 120**)



Neuropsychiatric symptoms (Neuropsychiatric Inventory **12-item, score from 0 to 144**)



Nutritional status (mini-nutritional assessment)