Exercise effects on falls, fractures, hospitalizations and mortality in older adults with dementia: an individual-level patient data meta-analysis

Short title: **Exercise effects in older adults**

Philipe de Souto Barreto, PhD[1,2], Mathieu Maltais, PhD[1], Erik Rosendahl, PhD[3], Bruno Vellas, MD[1,2], Isabelle Bourdel-Marchasson, MD[4], Sarah E Lamb, PhD[5], Kaisu Pitkala, MD[6], Yves Rolland, MD[1,2]

1: Gerontopole of Toulouse, Institute of Ageing, Toulouse University Hospital (CHU Toulouse), Toulouse, France; 2: UPS/Inserm UMR1027, University of Toulouse III, Toulouse, France; 3: Department of Community Medicine and Rehabilitation, Physiotherapy, Umeå University, Sweden; 4: CNRS/Université de Bordeaux, UMR 5536 Résonance Magnétique des systèmes Biologiques, Bordeaux, France; 5: Exeter Medical School, University of Exeter, UK. 6: Department of General Practice, University of Helsinki, Helsinki, Finland.

Corresponding author: Professor Philipe de Souto Barreto, Gérontopôle de Toulouse, Institut du Vieillissement, 37 Allées Jules Guesde, F-31000 Toulouse, France

Phone: (+33) 561 145 668

Fax: (+33) 561 145 640

e-mail: philipebarreto81@yahoo.com.br

Word count: 4323

Abstract

Background/Objective. To study the effects of exercise on falls, fractures, hospitalizations and death in people with dementia.

Methods. We conducted an individual-level patient data meta-analysis of seven randomized controlled trials (RCT). We looked for studies from the reference list of previous systematic reviews and undertook an electronic search for articles published between 2013 and 2019 in Ageline, CENTRAL, PsycINFO, PubMed, and SportsDiscus.

Main outcome measures. Main (binary) outcome measures were the risk of mortality; hospitalization; faller; multiple faller; injurious faller; and fractures. Secondary (count) outcomes were the incident rates of hospitalizations, falls, and injurious falls.

Results. From the 1,314 participants, 771 were allocated to the exercise group and 543 to the control group. The number of cases regarding the main outcome measures in exercisers and controls were, respectively: 45 (5.8%) and 31 (5.7%) deaths; 102 (14.4%) and 65 (13.4%) participants hospitalized; 221 (34.4%) and 175 (41.3%) had at least one fall; 128 (20.2%) and 92 (21.7%) had multiple falls; 78 (24.8%) and 92 (29.3%) had injurious falls; and 19 (2.9%) and 15 (3.5%) had suffered a fracture. Two-step meta-analysis found no effects of exercise on any outcome. One-step meta-analysis found exercise reduced the risk of falls (OR 0.75; 95%CI 0.57–0.99). Exploratory analysis showed exercise decreased the rate of incident falls in participants with the lowest functional ability (IRR 0.48; 95%CI 0.30–0.79).

Conclusions and Relevance. Although the two-step meta-analysis suggests exercise does not have an effect on the outcomes, one-step meta-analysis suggested that exercise may reduce fall risk. Data from further high-quality RCTs is still needed.

Key-words: exercise; adverse events; falls; dementia;

Introduction

Exercise is one of the most important non-pharmacological interventions used for the management of dementia(1). Previous systematic reviews and meta-analyses have suggested that exercise training may benefit people with dementia in terms of depression, activities of daily living (ADL), and even cognitive function(2–5).

However, meta-analysis of the effects of exercise RCTs in people with dementia on the important clinical outcomes falls, fractures, hospitalizations and death are almost non-existent. To the best of our knowledge, no meta-analysis of exercise in dementia gathered data on fractures, hospitalization and death. The biological mechanisms through which exercise may counteract the deleterious effects of aging (in particular in the central nervous system and musculoskeletal) and, then, lead to risk reductions on falls and fractures are multiple and probably involve positive effects against sarcopenia(6) (eg, great muscle fiber area(7), muscle mitochondria functioning(8), as well as other mechanisms(9,10)), bone health(11) maintenance/improvements of muscle strength(12–17), mobility(12,16), stability, and balance control (14,16,18). In turn, decreasing falls and fractures might bring forth benefits on other clinical outcomes since these events often lead to hospitalization(19–21) and may lead to death(22).

Only one meta-analysis(23), using aggregated data of two randomized controlled trials (RCT), investigated exercise effects on falls and reported a positive effect for reducing both the mean number of falls and the risk of being a faller. Several methodological limitations in original investigations of exercise training for people with dementia impede solid conclusions and render it difficult to undertake robust meta-analysis. Most studies have small samples (median number of participants randomized among studies included in previous systematic reviews ≤ 40(2–5)); and are often rated as having high-risk of bias. No individual-level patient data (IPD) meta-analysis, gathering data of large-scale, high-quality exercise RCTs in people with dementia, has been undertaken to date. IPD meta-analysis has several advantages, in particular, the possibility to explore optimal intervention doses (e.g, exercise frequency) and interactions between participants' characteristics (e.g, dementia severity, levels of functional decline) and intervention in order to identify target populations that would benefit the most from exercise. The best exercise dose for people with dementia and specific characteristics of the population that may benefit the most from exercise is still unknown; limited data from several populations of older adults, including from nursing homes, suggests that a frequency between twice and thrice a week(24,25) could be optimal.

The objectives of the present IPD meta-analysis of RCTs for people with dementia were to investigate the effects of exercise on mortality, falls, fractures, and hospitalizations and explore elements of exercise regime (e.g, weekly frequency) as well as if individuals' characteristics that might moderate the findings.

Methods

This study has been registered in the publicly accessible database PROSPERO (number: CRD42019124486) and follows the PRISMA guidelines(26).

Eligibility Criteria

Inclusion criteria were: (a) RCT with supervised exercise as (one of) the intervention(s); (b) study population composed of older individuals with dementia (mean age of study population ≥ 65 years); (c) the original investigation compared the exercise intervention(s) with a non-exercise comparator group; (d) the study had available data on at least one of the outcome measures of the present meta-analysis; (e) moderate-to-large sample size, as defined by having randomized > 80 subjects (ie, the mean sample size from a recent systematic review of exercise in dementia(2) involving 20 studies). This latter criterion was applied because large exercise trials have better methodological appraisal than small-scale studies(2,3,27) and provide more accurate findings(27). When applied to recent meta-analyses of exercise RCTs for people with dementia(2,3), the cut-off of 80 participants discriminated studies at low risk of bias from those at high risk.

All kinds of supervised (e.g, healthcare professionals or caregivers) exercises (e.g, home-based or group-based) were eligible.

Search Strategy

We screened articles from recently published meta-analysis of exercise RCTs for people with dementia(2–4). From these reviews, two authors independently selected articles that matched the eligibility criteria. Because the last date searched by Forbes et al.(3) in their Cochrane review was in the year 2013, one author undertook a search on February 5th 2019, from January 2013 to present at: Ageline, Cochrane Central Register of Controlled Trials, PsycINFO, PubMed and SportsDiscus (Supplements). No language restrictions applied. One author screened title/abstract to remove studies completely out of scope; then, two authors assessed the full-text of potentially eligible articles independently. Both first and corresponding authors of eligible studies were then contacted by e-mail to ask for the raw data; up to three reminder e-mails over two weeks were sent.

Outcome measures

Binary (primary) outcomes were: Mortality; Hospitalization (eg, inpatient hospitalization, ≥24hr hospitalization); Faller (ie, ≥ 1 fall); Multiple faller (ie, ≥ 2 falls); Injurious faller (ie, ≥ 1 injurious fall: eg, fall with wound, head trauma, medical care, fracture, hospitalization); and Fractures (≥ 1 fracture). Count outcomes were: number of hospitalizations, number of falls, and number of injurious falls.

Data on all outcome measures were obtained during the intervention length; to avoid the potential bias related with additional confounders modifying the associations between exercise and the outcomes, data from observational period (often less controlled than the intervention period) obtained after the end of the intervention were not selected.

Data extraction

The corresponding authors of original investigations selected and extracted the required data. Data was checked for consistency by looking at the published original investigations and discussions with original investigators. Beyond the outcome measures, and to keep consistency across RCTs, we selected the following baseline data: age (years), sex, cognitive function (using the Mini-Mental State Examination (MMSE)(28), score range 0-30, higher is better), ADL performance (standardized score), intervention allocation (exercise VS. controls), exercise regimen (i.e, weekly frequency, intensity, session duration, exercise type), exercise adherence (exercise sessions attended/ sessions proposed * 100), and study length (weeks). Effective exercise weekly frequency was obtained as follows: (exercise adherence * exercise weekly frequency proposed)/100.

The following categorical variables were created: age (≤75; 75-85; >85 years); effective frequency (<1x/week; 1-2x/week; >2x/week), dementia severity (MMSE score: mild dementia, ≥21; moderate dementia, 16-20; moderate to severe dementia, 11-15; severe dementia, ≤10), ADL performance into quartiles.

Risk of bias

This was assessed independently by two authors across the seven domains of the Cochrane Collaboration risk of bias tool(29).

Statistical analysis

As pre-specified in the protocol (Supplements), we employed both two-step and one-step approaches for the meta-analysis. Thirty-seven individuals had < 65 years; since analyses performed with and without these individuals did not change the results, they were kept in the final dataset.

The two-step approach was the primary analysis. The statistical plan was modified due to missing data regarding the date of the events (missing data > 20% across all outcomes).

Therefore, we opted for using a 2x2 table as the primary analysis for binary outcomes (instead of survival analysis), which were combined in relative risk (RR) using both DerSimonian and Laird's random-effects(30) and fixed effect model (with Mantel-Haenszel method). When heterogeneity, which was evaluated using I^2 statistics, was substantial, ie, $I^2 > 50\%$(31), the main analysis was performed using random-effect, whereas fixed-effect models were run when $I^2 \leq 50\%$. The 2x2 aggregate data approach have the advantage of not being vulnerable to within-study analysis issues, such as perfect failure prediction (when 0% of the outcome occurs among either the experimental or the control groups). The intra-cluster correlation (ICC) coefficient was obtained from a logistic regression model for each cluster RCT, and was employed to calculate the effective sample size using the design effect. Bias was assessed using the Egger's test, with $p<0.1$ indicating important asymmetry, and funnel plots. For count data, we first performed within-study Poisson or negative binomial regressions, as appropriate. Then, the coefficients and 95%CI were combined using the inverse variance method (both random and fixed models).

In the one-step approach, for both binary and count outcomes, we pooled the samples across all included RCTs. Binary outcomes were analyzed using a mixed-effect logistic regression with group allocation, sex, age, ADL performance and MMSE as fixed terms and a study level random-effect. For count data, mixed-effect Poisson or negative binomial models were performed with the same fixed and random effects.

For all count analyses, we defined the exposure variable as the total length of the intervention period for each participant individually (days) (baseline to post-intervention or death interval).

For all outcomes, we performed stratified analysis according to study setting (community-dwelling or long-term care facility (LTCF)) and as a function of the type of control group (active controls or usual care); these analyses are available in Supplements. All analyses were performed using STATA version 14 (College Station, TX: StataCorp LP) and a $p<0.05$ applied for statistical significance.

Sensitivity Analysis in the two-step approach

Within-study binary logistic regressions with group allocation (exercise VS. controls) and further adjusted for age, ADL performance, MMSE and sex. For cluster RCTs, sensitivity analysis used mixed-effect binary logistic regression with the same fixed effects, and a random effect at the cluster level. One of the cluster RCTs(32) was further adjusted for nutritional status and neuropsychiatric symptoms due to baseline imbalance between groups. The log natural of the OR were then combined across studies using the inverse variance method (both random and fixed models).

Sensitivity Analysis in the one-step approach

For both count and binary outcomes, a sensitivity analysis was performed by removing from the model people with an effective weekly exercise frequency <1x/week, since such a low frequency is unlikely to lead to benefits on the endpoints investigated.

Exploratory analysis

To get insights on the populations that would benefit the most from exercise, we tested interaction terms between group allocation and: age (categorical), sex, dementia severity, and ADL performance (in quartiles).

Results

The authors of 14 studies were contacted: seven provided their data, two indicated they did not collect data on any of our outcome measures, and five did not answer. Table 1 describes study characteristics of the seven included RCTs(32–38). Three of them came from France, two from Sweden, one from the UK, and one from Finland. Length of intervention varied from 13 to 52 weeks. Five trials were performed in long-term care (32–34,37,38) and two in community-dwelling settings(35,36). Three trials (32,37,38) were cluster-randomized, and four(33–36) had parallel individual randomization. Two studies(34,35) had two different exercise interventions; for the purposes of the meta-analysis, they were combined into a single exercise group. One trial(37) had a 2x2 factorial design (exercise, nutrition, exercise + nutrition, and controls); the two exercise groups were combined as well as the two non-exercise groups. Two RCTs(34,37) had the study population composed of a mix of individuals with and without dementia; the data used in this meta-analysis corresponded only to people with dementia. All studies, but one(34), diagnosed dementia using established standards at the moment the trial was run; for the study(34) that did not formally diagnosed dementia, we selected individuals with a MMSE $\leq$ 23 (this trial only provided data for mortality; analysis removing participants of this RCT were performed). RCTs randomized between 97 and 494 participants. Comparator groups were active controls for three trials(32,37,38) and usual care for the other four trials(33–36). The exercise interventions were supervised multicomponent training (ie, different exercise types during the same session, such as aerobic, muscle strength, balance and coordination), with proposed weekly frequency between two and four times a week, intensity from moderate to vigorous, and exercise session duration ranged from 30 to 90 minutes per session.

Risk of bias was overall low, except regarding blinding of participants and personnel, which is an inherent issue for most RCTs of behavioral interventions.

We obtained data for 1314 participants with dementia, being 543 (41.3%) allocated to control groups and 771 (58.7%) to exercise. Table 2 shows participants' characteristics for the pooled population according to group allocation. The sample size varied according to the outcome investigated.

Mortality

All seven trials provided data for mortality, with only one study having no deaths(37). Seventy-six deaths (5.8%) occurred during the intervention period. For the 2x2 table in the two-step approach, exercise had no effects on mortality in both fixed- (see Figure 1A; p=0.99) and random-effect models. Heterogeneity was absent (I^2=0%), but the Egger's test detected asymmetry (p=0.007); the funnel plot showed that smaller studies favored the control group (less deaths), whereas larger studies favored exercisers. Removing the study by Dechamps et al.(34), since it did not use established standards to diagnose dementia, attenuated the asymmetry without changing the results. Sensitivity analysis combining the log natural of OR of each study provided similar non-significant results (ES: 0.85; 95%CI: 0.48 – 1.51; p=0.59; I^2=15.3%. One trial(34) was removed because the within-study binary logistic regression presented the issue of perfect failure prediction (0% of deaths occurred among controls)).

For the one-step approach, compared to the control group, exercise did not reduce mortality (OR 1.06; 95%CI 0.63 – 1.80; p=0.82). The sensitivity analysis removing exercisers with effective frequency <1x/week remained insignificant (OR 0.76; 95%CI 0.41 – 1.41; p=0.39).

Hospitalization

Six trials(32,33,35–38) had data on hospitalizations. Among the 1192 participants, 167 (14.0%) have been hospitalized. Meta-analysis using the 2x2 table showed no effect of exercise on hospitalization in both fixed- (Fig 1B; p=0.45) and random-effect models. Heterogeneity was low (I^2=3%), and no asymmetry was identified (Egger's test: p=0.53). Sensitivity analysis combining OR (log natural) across studies gave unchanged non-significant results (ES: 1.21; 95%CI: 0.80 – 1.83; p=0.37; I^2=2.5%. Note that due to the issue of perfect failure prediction (0% of hospitalizations occurred among controls), one study(36) was removed).

For the one-step approach, compared to the control group, exercise was not associated with hospitalization (OR 1.17; 95%CI 0.80 – 1.73; p=0.42). The sensitivity analysis removing exercisers with low effective frequency changed the direction of the association, but remained non-significant (OR 0.98; 95%CI 0.65 – 1.50; p=0.94).

Only four RCTs reported the number of hospitalizations(32,33,35,36) (n=906): 59 people (6.5%) had only one hospitalization and 72 (7.9%) had two or more. Combining data across studies in a two-step approach found no effects of exercise on the outcome in both fixed- and random-effect (Fig 1C; p=0.28). One-step analysis provided similar findings (IRR 1.38; 95%CI 0.92 – 2.07; p=0.12); analysis removing people with low effective frequency attenuated the magnitude of association (IRR 1.06; 95%CI 0.70 – 1.62; p=0.77), but remained statistically non-significant.

Falls and Multiple falls

Five trials(32,35–38) had available data on falls. Among the 1066 individuals, 396 (37.2%) have suffered a fall. The 2x2 table approach showed near to significant association of exercise with falls in both fixed- (Fig 2A; p=0.091) and random-effect models. Heterogeneity was moderate (I^2=45.4%). No asymmetry was observed (Egger's test: p=0.95). Sensitivity analysis combining within-study OR (log natural) provided similar results (ES: 0.79; 95%CI: 0.59 – 1.06; p=0.11; I^2=47.2%).

In one-step approach, compared to controls, exercisers had a significant 25% lower probability of suffering a fall (OR 0.75; 95%CI 0.57 – 0.99; p=0.040). The sensitivity analysis removing exercisers with low effective frequency found similar results, but lost significance (OR 0.79; 95%CI 0.59 – 1.05; p=0.10).

Regarding the number of falls, 176 people (16.5%) had only one fall and 220 (20.6%) had two or more. Combining data using a two-step approach found exercise had a non-significant association with the outcome in both fixed- and random-effect (Fig 2B; p=0.33) models. One-step analysis gave a similar result (IRR 0.82; 95%CI 0.63 – 1.06; p=0.13). Analysis removing people with <1x/week effective frequency showed exercisers had significant lower IRR for falls compared with controls (IRR 0.76; 95%CI 0.59 – 0.99; p=0.039).

For multiple falls, the 2x2 table approach found no effect of exercise on this outcome in both fixed- and random-effect (Fig 2C; p=0.71) models. Heterogeneity was substantial (I^2=52.2%). No asymmetry was observed (Egger's test: p=0.60). Sensitivity analysis combining within-study OR (log natural) provided similar results (ES: 0.87; 95%CI: 0.49 – 1.55; p=0.64; I^2=55.6%).

In one-step approach, exercise was not significantly associated with multiple falls (OR 0.82; 95%CI 0.59 – 1.13; p=0.23). The sensitivity analysis removing exercisers with <1x/week effective frequency did not change the results (OR 0.85; 95%CI 0.61 – 1.18; p=0.34).

Injurious falls and Fractures

Four RCTs(32,35,37,38) provided information on injurious falls. From the 574 participants, 154 (26.8%) had an injurious fall. Meta-analysis using 2x2 data found a near-to-significant association of exercise with injurious falls in both fixed- (Fig 3A; p=0.09) and random-effect models. Heterogeneity was I^2=0% and there was no asymmetry (Egger's test: p=0.50). Sensitivity analysis combining within-study OR (log natural) provided similar findings (ES: 0.75; 95%CI: 0.50 – 1.13; p=0.17; I^2=0%).

In the one-step approach, a similar near-to-significant association was found between exercise and injurious fall (OR 0.71; 95%CI 0.48 – 1.05; p=0.089). The sensitivity analysis removing exercisers with low effective frequency attenuated this association (OR 0.75; 95%CI 0.50 – 1.12; p=0.16).

Regarding the number of injurious falls, from the 574 participants with available data, 102 (17.6%) had one injurious fall and 52 (9.1%) had two or more. Combining data using a two-step approach found exercise had a non-significant association with the outcome in both fixed- and random-effect (Fig 3B; p=0.49) models. One-step meta-analysis provided unchanged results (IRR 0.81; 95%CI 0.57 – 1.16; p=0.25), including the sensitivity analysis removing people with low effective exercise (IRR 0.82; 95%CI 0.57 – 1.18; p=0.29).

For fractures, five studies(32,35–38) had patient-level data available. From the 1069 people, 34 (3.2%) suffered a fracture (only two individuals suffered more than one event). Exercise was not associated with this outcome in both fixed- (Fig 3C; p=0.83) and random-effect models. Heterogeneity was I^2=0%. No asymmetry was observed (Egger's test: p=0.49). One further trial(33) did not have patient-level data available, but we could obtain the aggregated data from the original report; including this trial in the 2x2 aggregated analysis did not modify the findings. Due to issues of perfect prediction, we did not combined data using the log natural of within-study ORs.

For the one-step approach, exercise had no effect on fractures (OR 0.91; 95%CI 0.45 – 1.85; p=0.80). Analysis removing exercisers with low effective frequency provided unchanged findings (OR 0.93; 95%CI 0.45 – 1.95; p=0.86).

Analysis stratified by study setting (community-dwelling or LTCF) and control group (active controls or usual care)

Stratified analysis provided mostly non-significant results (Supplements, Appendix 11 and Appendix 12 for setting and control group analyses, respectively), except: in LTCF, exercisers had an increased IRR for the number of hospitalizations (n=210 from two studies(32,33)); in studies among community-dwellers and with usual care controls, exercisers had a reduced IRR for both the number of falls (n=583 from two studies(35,36)) and injurious falls (n=191 from one study(35)).

Exploratory analysis

Most analyses exploring the interactions between the intervention and participants' characteristics (ie, ADL levels, dementia severity, age, and sex) provided non-significant associations for all the outcomes, except for: sex (interaction: IRR 0.40; 95%CI 0.18 , 0.91; p= 0.028), with women (but not men) in the exercise group having a higher incident rate ratio (IRR) of hospitalizations (IRR 2.13; 95%CI 1.20 – 3.79; p=0.010) than those in the control group; and ADL levels, with exercisers in the lowest ADL quartile (worst function) having a lower IRR for falls (IRR 0.48; 95%CI 0.30 – 0.79; p=0.003), compared to controls in the same ADL quartile (no significant associations were found for the remaining three ADL quartiles).

Discussion

The primary analysis (two-step approach) did not support exercise has positive effects on the outcomes investigated. Secondary analysis using the one-step (pooled) approach found that exercise was associated with a reduced risk of fall. Findings on injurious falls suggest exercise may reduce injurious falls, although this was not statistically significant and hence should be interpreted with caution. Exercise had no effects on death, hospitalization, multiple falls, and fractures.

Our primary analysis found only a near-to-significant (p=0.091) association with the risk of falls; however, this result, allied to the significant finding from the one-step analysis suggest that the well-known association of exercise with fall reduction(24,39,40) in older people potentially applies to the specific population of people with dementia. This assumption is further supported by recent literature indicating the one-step approach to IPD meta-analysis may outperform the traditional two-step approach(41,42), even though there is no consensual gold standard defining the best approach in IPD meta-analysis. Previous meta-analyses in people with dementia(23) or cognitive impairment(43) found exercise benefited participants on fall-related outcomes. The present work extends findings from prior meta-analysis by including a higher number of studies and sample size, and by having access to the individual-level patient data.

Findings from our exploratory and sensitivity analyses further extend the literature by suggesting exercise reduces the rates of incident falls in individuals with the highest risks (participants with low functional ability). Focusing the exercise intervention in subjects with very low functional ability may be a beneficial strategy; in our dataset, subjects in the worst ADL performance group had: ADCS-ADL-sev ≤ 12 (mean (±SD), 7.4 (2.9))(32); Barthel Index (0-20 points) ≤ 10 (5.7 (2.1))(37,38); Functional Independence Measure ≤ 59 (47.7 (10.3))(35); Bristol ADL index ≥ 18 (24.1 (5.9)(36)). The information that exercising ≥ 1x/week might bring about reductions in the number of falls deserves further investigation, since keeping higher effective exercise frequencies in the long term may be challenging in such a vulnerable population(25,44). The possibility that very high weekly frequencies of exercise would increase the risk of falls, as raised by previous studies(24,45), seems not to apply to people with dementia for weekly frequencies lower than 4x/week (maximum frequency across studies included in this meta-analysis). Why the exercise interventions had no effects on multiple falls deserves further investigations. A recent study on exercise plus home hazard reduction(46) found the intervention decreased by 26% the number of multiple faller in people with cognitive impairment. It is, however, possible that multiple falls is a difficult-to-change outcome that would ask for individualized exercises specifically tailored to reduce falls or the combination of exercise with other interventions. Once further high-quality RCTs, with different exercise intensities, frequencies, and duration will be available for pooled analysis, this hypothesis can be tested.

Previous meta-analyses (24,39,47) have consistently found exercise reduces the risk and/or incident rates of injurious falls in older people. Our results among people with dementia point in this direction, although not statistically significant; the absence of significant associations was probably related to lack of power for this analysis. The significant reduction in the number of injurious falls in community-dwellers must be examined with caution since this analysis involved only one study. Injurious falls is a major clinical event and interventions that may affect this outcome in individuals with dementia, such as exercise, should systematically report on it.

It is interesting to note that, even though not significant, our primary analyses on the associations of exercise with fallers and injurious fallers follow similar patterns than those found in previous high-quality meta-analyses not restricted to people with dementia.(24,39,40,47), with modest benefits for the risk of being a faller (reduced risk of 11%-17%; 13% in this study) and moderate benefits for the risk of injurious faller (reduced risk > 20%; 21% in this study). If such effects are confirmed when further data from high-quality exercise RCTs in people with dementia are added, this may mean that exercise benefit people with dementia to the same extent than it does to other populations of older people. It is therefore possible that dementia is not in itself a barrier that would impede individuals to benefit from exercise in terms of risk reduction for falls.

Regarding fracture, this was an extremely rare event in our sample and the issue of statistical power may, therefore, have affected analysis on this outcome. The literature on exercise effects for decreasing the risk of fractures in older people is still mixed(24,40,48,49); data is lacking for exercise RCTs in dementia populations.

The non-significant associations with mortality and hospitalization were expected, since this is in-line with literature on this topic (24,39). For hospitalizations, although far from significance, the fact analyses showed exercise was associated with increased risk and incidence rate for this outcome is troubling. The interaction between intervention and sex, with women exercisers having higher incident rate of hospitalizations than women in control group, as well as the stratified analysis in LTCF showing that exercisers had an increased number of hospitalizations compared to controls, ask for further research on this topic.

The present study has several strengths: this is the first IPD meta-analysis ever undertaken regarding exercise RCTs for people with dementia. Since we had access to raw data, we could explore hypothesis about the best exercise dose (weekly frequency really performed by participants) and the target population; we selected clinically meaningful outcomes; sample size was large for this research field, potentially reducing power-related bias. However, limitations are worth mentioning: due to heterogeneity across RCTs, we were unable of stratifying analysis according to dementia subtype and dementia diagnosis criteria, and further adjusting analysis for potential confounders; data on the number of hospitalizations and injurious falls were less often available, diminishing the statistical power and reducing findings' generalizability; although sample size was large, we probably lacked power for analysis on mortality and fractures, as well as stratified analysis according to study setting; analyses were not corrected for multiple comparisons, thus, multiplicity may have increased the chances of type I error. The choice for including RCTs with > 80 participants was arbitrary. Gathering data from all trials and undertaking subgroup analysis restricted to large-scale and high-quality RCTs would have been a more comprehensive approach; however, it would have been much more time- and resource-consuming. Although this sample size criterion was arbitrary, this led to the inclusion of high-quality trials with reliable data and, then, robust results.

Conclusions

Our primary (two-step) analysis suggests that exercise does not have an effect on falls, injurious falls, fractures, hospitalization or mortality in individuals with dementia during the intervention period. One-step analysis showed exercise was associated with a reduced risk of falls. These mixed findings demonstrate the difficulty in drawing solid conclusions for the moment about the benefits of exercise on these important outcomes in people with dementia. Further large-scale, high-quality RCTs are still needed to explore the potential for exercise to decrease the risk of both falls and injurious falls in this population. Future exercise RCTs in individuals with dementia should systematically collect and report (including count) data on crucial outcomes, such as injurious falls, hospitalizations and fracture, besides more classical data on mortality and falls.

Authors contribution

Philipe de Souto Barreto conceived and wrote the protocol, provided data for the meta-analysis, performed the statistical analysis, interpreted data, drafted the article, and approved its final version.

Mathieu Maltais contributed to the protocol, organized the master dataset and checked it for consistency, interpreted data, critically reviewed the article for important intellectual content, and approved its final version.

Erik Rosendahl provided data for the meta-analysis, checked data for consistency, interpreted data, critically reviewed the article for important intellectual content, and approved its final version.

Isabelle Bourdel-Marchasson provided data for the meta-analysis, checked data for consistency, interpreted data, critically reviewed the article for important intellectual content, and approved its final version.

Bruno Vellas interpreted data, critically reviewed the article for important intellectual content, and approved its final version.

Sarah Lamb provided data for the meta-analysis, checked data for consistency, interpreted data, critically reviewed the article for important intellectual content, and approved its final version.

Kaisu Pitkala provided data for the meta-analysis, checked data for consistency, interpreted data, critically reviewed the article for important intellectual content, and approved its final version.

Yves Rolland contributed to the protocol, provided data for the meta-analysis, checked data for consistency, interpreted data, critically reviewed the article for important intellectual content, and approved its final version.

Declaration of interest. Authors declare no conflicts of interest related to this article. Conflicts of interest unrelated to this article: **PSB** – none; **MM** – none; **ER** – none; **IB-M** – none; **BV** was Scientific Board member for: Acadia, Accera, Biogen, Lilly, Lundbeck, MSD, Nestlé, Roche, Takeda, Transition Therapeutics, Otsuka, Schwabe. He received lecture fees from Novartis and obtained grant support from ABBVIE, ACCERA, ALZHEON, ASTRA ZENECA, BIOGEN, ELI LILLY, LUNDBECK, LPG SYSTEMS, MERCK, NESTLE, OTSUKA, PFIZER, PIERRE FABRE, SANOFI, and SERVIER; **SEL** - none; **KP** – none; **YR** - none.

Acknowledgments

Funding

This meta-analysis did not receive any external funding. Financial support for the original investigations included in the present work were: *de Souto Barreto et al.*(13) – Mission Recherche from the Direction de la Recherche, des Etude, de l'Evaluation et des Statistiques (MiRE-DREES) and Caisse Nationale de Solidarité pour l'Autonomie (CNSA); *Rolland et al.*(14) – CNSA; *Dechamps et al.*(15) – Association de Recherche Gérontologique and Region Nouvelle Aquitaine; *Pitkälä et al.*(16) – FINALEX study was supported by the Social Insurance Institution of Finland, the Central Union for the Welfare of the Aged, the Sohlberg Foundation, and King Gustaf V and Queen Victoria's Foundation; *Lamb et al.*(17) – DAPA was funded by the National Institute for Health Research (NIHR Health Technology Assassment programme) and received additional funding from the NIHR Local Clinical Research Networks and NIHR Oxford CLAHRC and Biomedical Research Centre; *Rosendahl et al.*(18) – the Swedish Research Council (grant numbers K2002-27VP-14165-02B, K2002-27VX-14172- 02B, K2005-27VX-15357-01A), the Swedish Council for Working Life and Social Research, the Ragnhild and Einar Lundström's Memorial Foundation, the Swedish Dementia Association, the Vårdal Foundation, the Gun and Bertil Stohne Foundation, the Erik and Anne-Marie Detlof's Foundation, and the Borgerskapet in Umeå Research Foundation; *Toots et al.*(19) – the Swedish Research Council (grant numbers K2009-69P-21298-01-4, K2009-69X-21299-01-1, K2009-69P-21298-04-4, K2014-99X-22610-01-6); Forte – Swedish Research Council for Health, Working Life and Welfare; the Vårdal Foundation; the Swedish Dementia Association; the Promobilia Foundation; the Swedish Society of Medicine; the Swedish Alzheimer Foundation; the King Gustav V and Queen Victoria's Foundation of Freemasons; the European Union Bothnia-Atlantica Program; the County Council of

Västerbotten, the Umeå University Foundation for Medical Research; the Ragnhild and Einar Lundström's Memorial Foundation; and the Erik and Anne-Marie Detlof's Foundation.

Role of the funding source. Funders had no role in the present work. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

References

1. Alzheimer’s Association. 2016 Alzheimer’s disease facts and figures. Alzheimers Dement J Alzheimers Assoc. 2016 Apr;12(4):459–509.

2. Barreto P de S, Demougeot L, Pillard F, Lapeyre-Mestre M, Rolland Y. Exercise training for managing behavioral and psychological symptoms in people with dementia: A systematic review and meta-analysis. Ageing Res Rev. 2015 Nov;24(Pt B):274–85.

3. Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for people with dementia. Cochrane Database Syst Rev. 2015 Apr 15;(4):CD006489.

4. Groot C, Hooghiemstra AM, Raijmakers PGHM, van Berckel BNM, Scheltens P, Scherder EJA, et al. The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. Ageing Res Rev. 2016 Jan;25:13–23.

5. Du Z, Li Y, Li J, Zhou C, Li F, Yang X. Physical activity can improve cognition in patients with Alzheimer’s disease: a systematic review and meta-analysis of randomized controlled trials. Clin Interv Aging. 2018;13:1593–603.

6. von Haehling S, Morley JE, Anker SD. From muscle wasting to sarcopenia and myopenia: update 2012. J Cachexia Sarcopenia Muscle. 2012 Dec;3(4):213–7.

7. Moore DR, Kelly RP, Devries MC, Churchward-Venne TA, Phillips SM, Parise G, et al. Low-load resistance exercise during inactivity is associated with greater fibre area and satellite cell expression in older skeletal muscle. J Cachexia Sarcopenia Muscle. 2018;9(4):747–54.

8. Broskey NT, Greggio C, Boss A, Boutant M, Dwyer A, Schlueter L, et al. Skeletal muscle mitochondria in the elderly: effects of physical fitness and exercise training. J Clin Endocrinol Metab. 2014 May;99(5):1852–61.

9. Rong S, Wang L, Peng Z, Liao Y, Li D, Yang X, et al. The mechanisms and treatments for sarcopenia: could exosomes be a perspective research strategy in the future? J Cachexia Sarcopenia Muscle. 2020 Apr;11(2):348–65.

10. Pratt J, De Vito G, Narici M, Boreham C. Neuromuscular Junction Aging: A Role for Biomarkers and Exercise. J Gerontol A Biol Sci Med Sci. 2020 Aug 24;

11. Santos L, Elliott-Sale KJ, Sale C. Exercise and bone health across the lifespan. Biogerontology. 2017;18(6):931–46.

12. García-Molina R, Ruíz-Grao MC, Noguerón-García A, Martínez-Reig M, Esbrí-Víctor M, Izquierdo M, et al. Benefits of a multicomponent Falls Unit-based exercise program in older adults with falls in real life. Exp Gerontol. 2018;110:79–85.

13. Zhao R, Feng F, Wang X. Exercise interventions and prevention of fall-related fractures in older people: a meta-analysis of randomized controlled trials. Int J Epidemiol. 2017 01;46(1):149–61.

14. Beyer N, Simonsen L, Bülow J, Lorenzen T, Jensen DV, Larsen L, et al. Old women with a recent fall history show improved muscle strength and function sustained for six months after finishing training. Aging Clin Exp Res. 2007 Aug;19(4):300–9.

15. Karinkanta S, Heinonen A, Sievänen H, Uusi-Rasi K, Fogelholm M, Kannus P. Maintenance of exercise-induced benefits in physical functioning and bone among elderly women. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2009 Apr;20(4):665–74.

16. Iwamoto J, Suzuki H, Tanaka K, Kumakubo T, Hirabayashi H, Miyazaki Y, et al. Preventative effect of exercise against falls in the elderly: a randomized controlled trial. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2009 Jul;20(7):1233–40.

17. Englund DA, Price LL, Grosicki GJ, Iwai M, Kashiwa M, Liu C, et al. Progressive Resistance Training Improves Torque Capacity and Strength in Mobility-Limited Older Adults. J Gerontol A Biol Sci Med Sci. 2019 12;74(8):1316–21.

18. Halvarsson A, Oddsson L, Olsson E, Farén E, Pettersson A, Ståhle A. Effects of new, individually adjusted, progressive balance group training for elderly people with fear of falling and tend to fall: a randomized controlled trial. Clin Rehabil. 2011 Nov;25(11):1021–31.

19. Choi NG, Choi BY, DiNitto DM, Marti CN, Kunik ME. Fall-related emergency department visits and hospitalizations among community-dwelling older adults: examination of health problems and injury characteristics. BMC Geriatr. 2019 Nov 11;19(1):303.

20. Rau C-S, Lin T-S, Wu S-C, Yang JC-S, Hsu S-Y, Cho T-Y, et al. Geriatric hospitalizations in fall-related injuries. Scand J Trauma Resusc Emerg Med [Internet]. 2014 Nov 12 [cited 2020 Oct 31];22. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4232632/

21. Berry SD, Miller R. Falls: Epidemiology, Pathophysiology, and Relationship to Fracture. Curr Osteoporos Rep. 2008 Dec;6(4):149–54.

22. Burns E. Deaths from Falls Among Persons Aged ≥65 Years — United States, 2007–2016. MMWR Morb Mortal Wkly Rep [Internet]. 2018 [cited 2020 Oct 31];67. Available from: https://www.cdc.gov/mmwr/volumes/67/wr/mm6718a1.htm

23. Burton E, Cavalheri V, Adams R, Browne CO, Bovery-Spencer P, Fenton AM, et al. Effectiveness of exercise programs to reduce falls in older people with dementia living in the community: a systematic review and meta-analysis. Clin Interv Aging. 2015;10:421–34.

24. de Souto Barreto P, Rolland Y, Vellas B, Maltais M. Association of Long-term Exercise Training With Risk of Falls, Fractures, Hospitalizations, and Mortality in Older Adults: A Systematic Review and Meta-analysis. JAMA Intern Med. 2019 01;179(3):394–405.

25. de Souto Barreto P, Morley JE, Chodzko-Zajko W, H Pitkala K, Weening-Djiksterhuis E, Rodriguez-Mañas L, et al. Recommendations on Physical Activity and Exercise for

Older Adults Living in Long-Term Care Facilities: A Taskforce Report. J Am Med Dir Assoc. 2016 01;17(5):381–92.

26. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009 Jul 21;339:b2535.

27. Crocker T, Young J, Forster A, Brown L, Ozer S, Greenwood DC. The effect of physical rehabilitation on activities of daily living in older residents of long-term care facilities: systematic review with meta-analysis. Age Ageing. 2013 Nov;42(6):682–8.

28. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189–98.

29. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343:d5928.

30. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177–88.

31. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557–60.

32. de Souto Barreto P, Cesari M, Denormandie P, Armaingaud D, Vellas B, Rolland Y. Exercise or Social Intervention for Nursing Home Residents with Dementia: A Pilot Randomized, Controlled Trial. J Am Geriatr Soc. 2017 Sep;65(9):E123–9.

33. Rolland Y, Pillard F, Klapouszczak A, Reynish E, Thomas D, Andrieu S, et al. Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. J Am Geriatr Soc. 2007 Feb;55(2):158–65.

34. Dechamps A, Diolez P, Thiaudière E, Tulon A, Onifade C, Vuong T, et al. Effects of exercise programs to prevent decline in health-related quality of life in highly deconditioned institutionalized elderly persons: a randomized controlled trial. Arch Intern Med. 2010 Jan 25;170(2):162–9.

35. Pitkälä KH, Pöysti MM, Laakkonen M-L, Tilvis RS, Savikko N, Kautiainen H, et al. Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial. JAMA Intern Med. 2013 May 27;173(10):894–901.

36. Lamb SE, Sheehan B, Atherton N, Nichols V, Collins H, Mistry D, et al. Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. BMJ. 2018 16;361:k1675.

37. Rosendahl E, Gustafson Y, Nordin E, Lundin-Olsson L, Nyberg L. A randomized controlled trial of fall prevention by a high-intensity functional exercise program for older people living in residential care facilities. Aging Clin Exp Res. 2008 Feb;20(1):67–75.

38. Toots A, Wiklund R, Littbrand H, Nordin E, Nordström P, Lundin-Olsson L, et al. The Effects of Exercise on Falls in Older People With Dementia Living in Nursing Homes: A Randomized Controlled Trial. J Am Med Dir Assoc. 2019 Jul;20(7):835-842.e1.

39. Guirguis-Blake JM, Michael YL, Perdue LA, Coppola EL, Beil TL. Interventions to Prevent Falls in Older Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2018 24;319(16):1705–16.

40. Tricco AC, Thomas SM, Veroniki AA, Hamid JS, Cogo E, Strifler L, et al. Comparisons of Interventions for Preventing Falls in Older Adults: A Systematic Review and Meta-analysis. JAMA. 2017 07;318(17):1687–99.

41. Kontopantelis E. A comparison of one-stage vs two-stage individual patient data meta-analysis methods: A simulation study. Res Synth Methods. 2018 Sep;9(3):417–30.

42. Thomas D, Platt R, Benedetti A. A comparison of analytic approaches for individual patient data meta-analyses with binary outcomes. BMC Med Res Methodol. 2017 16;17(1):28.

43. Chan WC, Yeung JWF, Wong CSM, Lam LCW, Chung KF, Luk JKH, et al. Efficacy of physical exercise in preventing falls in older adults with cognitive impairment: a systematic review and meta-analysis. J Am Med Dir Assoc. 2015 Feb;16(2):149–54.

44. Vseteckova J, Deepak-Gopinath M, Borgstrom E, Holland C, Draper J, Pappas Y, et al. Barriers and facilitators to adherence to group exercise in institutionalized older people living with dementia: a systematic review. Eur Rev Aging Phys Act Off J Eur Group Res Elder Phys Act. 2018;15:11.

45. Sherrington C, Lord SR, Vogler CM, Close JCT, Howard K, Dean CM, et al. A post-hospital home exercise program improved mobility but increased falls in older people: a randomised controlled trial. PloS One. 2014;9(9):e104412.

46. Taylor ME, Wesson J, Sherrington C, Hill KD, Kurrle S, Lord SR, et al. Tailored exercise and home hazard reduction for fall prevention in older people with cognitive impairment: the i-FOCIS randomized controlled trial. J Gerontol A Biol Sci Med Sci. 2020 Sep 19;

47. El-Khoury F, Cassou B, Charles M-A, Dargent-Molina P. The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults: systematic review and meta-analysis of randomised controlled trials. BMJ. 2013 Oct 29;347:f6234.

48. Kemmler W, Häberle L, von Stengel S. Effects of exercise on fracture reduction in older adults: a systematic review and meta-analysis. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2013 Jul;24(7):1937–50.

49. Silva RB, Eslick GD, Duque G. Exercise for falls and fracture prevention in long term care facilities: a systematic review and meta-analysis. J Am Med Dir Assoc. 2013 Sep;14(9):685-689.e2.

Table 1. Study characteristics.

Authors and Year	Country	Study Design, Participants and groups	Exercise intervention	Dementia diagnosis	Setting	Comparator group
Dechamps et al. 2010(34)	France	*Design*: Parallel-group RCT; *Study population*: 82.3 yrs, 71.7% women, three groups: control n=60, multicomponent exercise group (CA)=49, adapted tai chi (AT) group n=51	Length. 24 weeks; Type. Group-based either multicomponent training or adapted tai chi; Intensity. Moderate in the multicomponent training and light-to-moderate in the adapted tai chi group; Frequency. twice a week in the multicomponent group and 4x/week in the adapted tai chi group; Session duration. 30-45 minutes for the multicomponent group and 30 minutes for the adapted tai chi group	MMSE ≤ 23	LCTF	Usual care
De Souto Barreto	France	*Design*: cluster-RCT; *Study population*: 87.7yrs, 82.5%	Length. 24 weeks; Type. Group-based multicomponent training (exercises to improve cardiorespiratory endurance, muscle strength, flexibility, and balance); Intensity.	DSM-IV	LTCF	Active controls: 24 weeks of group-based therapeutic music mediation (eg,

et al. 2017(32)		women, two groups: exercise (n=47), controls (n=50)	moderate; Frequency. twice a week; Session duration. 60 minutes.			relaxation, playing instruments, singing) or arts and crafts (eg, painting and drawing, clay modelling); 2x/ week, 60 min/session.
Lamb et al. 2018(36)	UK	*Design*: Parallel-group RCT; *Study population*: 78 yrs, 39% women, two groups: group-based exercise (n=329)[a], controls (n=165)	Length. Four months; Type. Multicomponent training (exercises to improve cardiorespiratory endurance and muscle strength); Intensity. Moderate-to-vigorous; Frequency. twice a week; Session duration. 60 to 90 minutes.	DSM-IV	Community dwelling	Usual care
Pitkala et al. 2013(35)	Finland	*Design*: Parallel-group RCT; *Study population*: 78 yrs, 39% women, three groups: home-based exercise supervised by physiotherapist (n=70), group-	Length. 52 weeks; Type. Multicomponent training (exercises to improve cardiorespiratory endurance, muscle strength, flexibility, and balance); Intensity. moderate; Frequency. twice a week; Session duration. 60 minutes	NINCDS-ADRDA	Community dwelling	Usual care

		based exercise (n=70)[b], controls (n=70)				
Rolland et al. 2007(33)	France	*Design*: Parallel-group RCT; *Study population*: 83 yrs, 75% women, two groups: exercise (n=67), controls (n=67)	Length: 52 weeks; Type. Group-based multicomponent training (exercises to improve cardiorespiratory endurance, muscle strength, flexibility, and balance); Intensity. moderate; Frequency. twice a week; Session duration. 60 minutes.	NINCDS-ADRDA	LTCF	Usual care
Rosendahl et al. 2008(37)	Sweden	*Design*: Cluster-RCT, 2x2 factorial design; *Study population*: 85 yrs, 73% women, two groups: exercise (n=91), controls (n=100); With-in each group, participants were randomized to receive either a nutrition intervention or placebo.	Length. 13 weeks; Type: Group-based, high-intensity functional exercise program (exercises to improve lower-limb strength, balance and mobility), individually-tailored and performed in weight-bearing positions similar to daily activities; Intensity: Moderate to high; Frequency: Five sessions per fortnight; Session duration. 45 minutes. At the end of the exercise period, physical tasks were introduced for the participant in order to maintain physical function	DSM-IV	LTCF	Active controls: 13 weeks of group-based activity program including activities performed while sitting, e.g., watching films, reading, singing, and conversing. The program was based on

						themes, e.g., the old country shop, famous people, and games from the past; 5 sessions per fortnight, 45 min/session.
Toots et al. 2019(38)	Sweden	*Design*: Cluster-RCT; *Study population*: 85 yrs, 76% women, two groups: exercise (n=93), controls (n=93)	Length. 17 weeks; Type: Group-based high-intensity functional exercise program (exercises to improve lower-limb strength, balance and mobility) individually tailored and performed in weight-bearing positions similar to daily activities; Intensity: Moderate to high; Frequency: Five sessions per fortnight; Session duration: 45 minutes	DSM-IV	LTCF	Active controls: 17 weeks of group-based activity program including activities performed while sitting, e.g., conversing, singing, listening to music or readings, looking at pictures and objects. The program was based on themes, e.g., local wild life, seasons, and holidays; 5

						sessions per fortnight, 45 min/session.

Note. DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; LTCF, long-term care facility; MMSE, Mini-Mental State Examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association; RCT, randomized controlled trial

[a] After the 4-month supervised exercise period, participants received a home-based physical activity program with a target of unsupervised 150 min/week of physical activity. Data for the current meta-analysis come from the supervised exercise period

[b] Home-based and group-based exercisers were combined in a single exercise group for the purposes of this meta-analysis

Table 2. Participants' characteristics

Variable	Total (n=1314)	Exercise group (n=771)	Control group (n=543)
Age (years)	80.8 (8)	80.1 (8)	81.9 (8)
Sex (women)	746 (56.8)	424 (55)	322 (59.3)
MMSE (0-30, higher is better)	17 (7)	17.7 (6.9)	16 (6.9)
ADL performance (quartiles), n=1,249			
Low	320 (25.6)	185 (25.4)	135 (26)
Intermediate low	312 (25)	184 (25.2)	128 (24.6)
Intermediate high	315 (25.2)	183 (25.1)	132 (25.4)
High	302 (24.2)	177 (24.3)	125 (24)
Exercise adherence (%), n=770	-	69.9 (30.3)	-
Effective weekly frequency (days/week)	-	1.5 (0.69)	-
Outcome measures			
Mortality (n=1313)	76 (5.8)	45 (5.8)	31 (5.7)
Hospitalization (n=1192)	167 (14.0)	102 (14.4)	65 (13.4)
Number of hospitalizations (n=906)	0.34 (1.09)	0.37 (1.16)	0.30 (0.98)
Falls (n=1066)	396 (37.1)	221 (34.4)	175 (41.3)
Number of falls (n=1066)	1.15 (3.1)	1.08 (3.1)	1.24 (3.1)
Multiple falls (n=1066)	220 (20.6)	128 (19.9)	92 (21.7)
Injurious falls (n=574)	154 (26.8)	78 (24.8)	76 (29.3)

Number of injurious falls (n=574)	0.46 (1)	0.44 (1)	0.48 (1)
Fractures (n=1069)	34 (3.2)	19 (2.9)	15 (3.5)

Note. Continuous variables are means (SD); categorical variables are absolute numbers (%).

Figures' Title

Figure 1. Effects of exercise on mortality, hospitalization, and rate of hospitalizations

Figure 2. Effects of exercise on falls, rate of falls, and multiple falls

Figure 3. Effects of exercise on injurious falls, rate of injurious falls, and fractures

Figure's Legends

Figure 1. Figure 1 displays the findings of the two-step meta-analysis on the risk of mortality (A), the risk of hospitalization (B), and the rates of hospitalizations (C).

Figure 2. Figure 2 displays the findings of the two-step meta-analysis on the risk of falls (A), the rates of falls (B), and the risk of multiple falls (people suffering ≥ 2 falls) (C).

Figure 3. Figure 3 displays the findings of the two-step meta-analysis on the risk of injurious falls (A), the rates of injurious falls (B), and the risk of fractures (C).