THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2018, Vol. 73, No. 11, 1504–1511
doi:10.1093/gerona/glx234
Advance Access publication 5 December 2017

OXFORD

Research Article

Exercise Training for Preventing Dementia, Mild Cognitive Impairment, and Clinically Meaningful Cognitive Decline: A Systematic Review and Meta-analysis

Philipe de Souto Barreto, PhD,[1,2] Laurent Demougeot, PhD,[3] Bruno Vellas, MD, PhD,[1,2] and Yves Rolland, MD, PhD[1,2]

[1]Gerontopole of Toulouse, Institute on Aging, Toulouse University Hospital (CHU Toulouse), France. [2]UMR INSERM 1027, University of Toulouse III, France. [3]Center of Genetics, Children's Hospital, Dijon, France.

Address correspondence to: Philipe de Souto Barreto, PhD, Gérontopôle de Toulouse, Institut du Vieillissement, 37 Allées Jules Guesde, F-31000 Toulouse, France. E-mail: philipebarreto81@yahoo.com.br

Received: September 25, 2017; Editorial Decision Date: November 15, 2017

Decision Editor: Anne Newman, MD, MPH

Abstract

Background: To assess the effects of long-term exercise on the onset of dementia, mild cognitive impairment (MCI), and other clinically meaningful cognitive decline in the elderly adults.

Methods: Systematic review with preplanned meta-analysis. Electronic searches were performed between November 2016 and May 2017. Randomized controlled trials (RCTs) examining the effects of long-term exercise (intervention length 12 months or longer) on the onset of dementia, MCI, or clinically meaningful cognitive decline in older adults without dementia at baseline were eligible. Two authors extracted the data independently. Four binary outcomes were defined: dementia onset, MCI onset, other clinically meaningful cognitive decline, and any of these three outcomes combined.

Results: Five studies (n = 2,878 participants randomized) were included in this review. Outcomes' incidence for exercisers and controls were, respectively: 3.7% (n = 949) and 6.1% (n = 1,017) for dementia (three studies), 10.2% (n = 686) and 9.1% (n = 682) for MCI (one study), 14.5% (n = 124) and 15.4% (n = 123) for other clinically meaningful cognitive decline (two studies), and 11.4% (n = 1,073) and 12.5% (n = 1,140) for all outcomes combined. Meta-analyses found no significant effects of exercise for reducing the risk of dementia, MCI, other clinically meaningful cognitive decline, or all outcomes combined.

Conclusions: Evidence from RCTs is limited and does not support that exercise reduces the risk of developing clinically important cognitive outcomes. Further long-term exercise RCTs are needed before solid conclusions can be drawn.

Keywords: Exercise, Cognitive function, Alzheimer, Randomized controlled trial

Physical activity (PA) has been consistently found to be associated with a reduced risk of developing dementia (regardless of its subtype), Alzheimer's disease, mild cognitive impairment (MCI), and clinically meaningful cognitive decline as shown in several systematic reviews and meta-analyses of longitudinal observational studies (1–4) as well as population-based analysis (5). However, the effects of exercise, a subtype of PA that is systematic, repetitive, and purposeful often employed to improve or maintain physical capacity and function, on the cognitive performance of older adults are still mixed (6,7). Two recent meta-analyses (12 randomized controlled trials [RCTs], n = 754 (6); and 25 RCTs, n = 2,217 (7)) of RCT in elderly individuals without known cognitive impairment found that aerobic exercise had no effects on the several cognitive functions analyzed, whereas Kelly et al.'s meta-analysis (7) provided limited evidence that resistance training (2 RCTs, n = 145 people included in the analysis) and Tai Chi (2 RCTs, n = 156 participants included in the analysis) slightly improved specific cognitive functions. Similar mixed results also apply to MCI, with meta-analyses overall showing no effects or small positive effects (8,9) on cognitive outcomes. However, most RCTs included in those meta-analyses had a medium- or small-term intervention length (usually 6 months or less), which may constitute a methodological limitation since persistent relevant

changes in cognitive function may require a longer time period, in particular for older people without known cognitive impairment.

Beside these inconsistent results, meta-analyses on the effects of exercise on cognition have used scores of scales (continuous variables) as cognitive outcomes; although sensitive to change and, therefore, appropriate for research purposes, those scales provide only limited information in terms of the clinical meaningfulness of cognitive changes. To the best of our knowledge, no meta-analysis has gathered data from RCTs of the effects of long-term (1 year or over) exercise interventions for preventing clinically relevant cognitive decline in the elderly adults.

The objective of this systematic review and meta-analysis of RCTs is to analyze the effects of long-term (1 year or over) exercise for preventing the onset of dementia, MCI, and clinically meaningful cognitive decline in older adult populations.

Methods

This systematic review and meta-analysis was registered in a publicly accessible registry, the PROSPERO database (registration number: CRD42016052690). Study report followed the PRISMA guidelines (10).

Eligibility Criteria

Articles meeting the following criteria were eligible for inclusion in this review:

1. RCTs in which the length of the exercise intervention lasted 1 year or longer. The 1-year intervention interval was established on the basis of clinical (we assumed that this time frame would constitute a sufficient interval to provide clinically meaningful information) and feasibility factors; indeed, although longer intervals would certainly lead to more clinically relevant information on cognitive decline, we have foreseen that very few exercise RCTs would have lasted more than 12 months;
2. The study must have compared the effects of one or more exercise interventions against a control group (usual care or an active-control group, including control sham exercise groups, such as stretching and light-intensity exercises (ie, exercises < 3 metabolic equivalent tasks (11) according with the Compendium of PA (12));
3. Study population must be composed of people with normal cognition (ie, without known cognitive impairment) or MCI. Studies in which population was composed of people with dementia were excluded;
4. Study population must be composed of people 60 years or over;
5. The study must have evaluated at least one of the outcomes of this review. All types of exercise interventions (type, frequency, intensity, duration) were eligible.

Search Strategy

One author performed the electronic searches between November 2016 and May 2017. We looked for articles in PubMed, the Cochrane Central Register of Controlled Trials (search performed for both databases on May 2, 2017), and PsychInfo/PsychArticles (search performed on November 29, 2016). The full search strategy is available in Supplementary Material (Protocol S-1). No language and publication date restrictions were used. Two raters performed title/abstract screening independently. After that, the full-text of potentially eligible studies was accessed. Divergences between raters on articles' eligibility were solved in a meeting (100% consensus on article eligibility was reached).

Outcomes

Four outcomes (all of them dichotomies) were defined: dementia onset (for cognitively intact people and MCI at baseline assessments), MCI onset (for cognitively intact people), clinically meaningful cognitive decline onset (for cognitively intact people and MCI), and onset of any of these three outcomes combined. The outcomes examined were assessed at the end of the intervention. The definitions of dementia, MCI, and clinically meaningful cognitive decline were identified in the original articles. For the outcome "clinically meaningful cognitive decline", our knowledge in the field of exercise RCTs in older adults led us to foresee that some studies would not have provided a clear definition for this outcome even if they assessed cognition. In such a case, and assuming that the Mini-Mental State Examination (MMSE) (13) would be the most used assessment tool for global cognitive function across studies, we set a two-point decline in the MMSE as a clinically relevant cut-off. Indeed, although no consensus exists on the minimum clinically relevant changes in the MMSE, authors have suggested that two- to four-point declines might represent true cognitive decline for older adults without dementia (14,15).

Data Extraction

For each study, two authors extracted the data independently using a standard data collection form. Divergences between raters were solved in a meeting (100% consensus regarding data extraction was reached). The first and/or corresponding authors of the included studies were contacted in the case data have been insufficiently reported in the original paper or to solve doubts reviewers had with regards to the data extracted.

Regarding group comparisons, we privileged comparisons made when the sole difference between groups was the exercise intervention. Studies with multidomain interventions, such as exercise training plus another intervention (eg, nutritional supplementation) compared to no intervention controls, were excluded from the review if reviewers considered that the nonexercise part of the intervention could impact any of the outcomes of this review.

Risk of Bias

The quality of included studies was assessed using the Cochrane Collaboration's tool for evaluating risk of bias (16). It assesses seven bias-related domains (sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other issues). For each of these domains, the risk of bias of studies was rated as low, high, or unclear.

Statistical Analysis

All outcomes of this study were binary. We combined the estimates for each study using the risk ratio (RR). Our knowledge about this research field led us to foresee a high heterogeneity across studies; therefore, we opted to use DerSimonian and Laird's random effects model (17) with Mantel-Haenszel method. Heterogeneity levels were assessed by visual inspection, and using the I^2 method ($I^2 > 50\%$ was considered substantial heterogeneity) (18). Small-study effects were evaluated using the Egger's test (regression of estimates against their standard error), with $p < .1$ indicating substantial asymmetry. Funnel plots were computed for visual input. For the outcome dementia

onset, we performed a sensitivity analysis by adding to the analysis data from Muscari et al. (19); although these authors have not formally diagnosed dementia in their study, they provided data for people who declined in the MMSE to a score between 20 and 23 at postintervention, scores that often characterize people with probable dementia (a MMSE score < 24 is overall accepted as dementia (20–24), even though the MMSE does not constitute a diagnostic tool (25)). For all outcomes, we undertook sensitivity analysis by using fixed effects instead of random effects when the meta-analysis included at least two studies and I^2 < 50%. The very small number of studies included in this meta-analysis impeded us to undertake preplanned sensitivity/subgroup analyses as described in the protocol.

When cluster RCTs were included, we looked for appropriated intracluster estimates from external databases (26–28). We then estimated the effective sample size for the cluster RCTs by dividing the sample size of the original study by the design effect. If no appropriate estimate was available, we presented unadjusted estimates. All analyses were performed using STATA version 14 (College Station, TX: StataCorp LP).

Results

From the 1,888 initial hits obtained through the electronic searches, only five studies (19,29–32) met eligibility criteria and had information/data on the outcomes of interest of this review. Supplementary Figure S1 displays the flowchart of studies. The characteristics of included studies are presented in Table 1. Two studies came from Hong Kong (the sole cluster-RCTs; intracluster estimates were not found in external databases. Therefore, unadjusted estimates were used for these trials) and one study came from each of Italy, United States, and Netherlands. Only one study had an intervention length higher than 12 months (31). All studies enrolled community-dwelling older adults, and one study also included people living in residential homes for the elderly adults (30). Three studies included only MCI (29,30,32), and the other two included people without dementia and/or with a MMSE ≥ 25. A total of 2,878 participants were randomized; sample size varied from 120 to 1,635 across studies. Two studies had more than two groups: Lam et al. (29) assigned participants to four groups, but only participants allocated to the exercise group alone and the social control group were included in this review and meta-analysis (people in the cognitive intervention group and cognitive + exercise group were excluded); whereas van Uffelen et al. (32) used a 2 × 2 design, with participants being allocated to walking + vitamin B, walking + placebo, sham exercise + vitamin B, and sham exercise + placebo: we combined the two walking groups (experimental participants) and the two sham exercise groups (control participants) and examined the whole study sample. Although van Uffelen et al. (32) did not report in their original publication any of the outcome measures of this review, authors had collected information on MMSE score and provided us with data on people who declined ≥ 2 points on this scale. The risk of bias (Supplementary Table S1) of included studies was globally low (high-quality studies): as for any behavioral intervention, the risk of blinding participants/personnel was high for almost all RCTs; allocation concealment may have been an issue for three studies (19,29,30); incomplete outcome data had a high risk for only one study (30).

Table 2 provides information on the exercise intervention and control group operationalized in the included studies. Exercise type varied: aerobic exercise in two studies, multicomponent training in other two studies, and Tai Chi in one study. Exercise sessions lasted from 30 to 60 min, and were performed from twice a week up to six times a week. In all studies, active control groups (instead of no intervention) were employed, with two studies using low-intensity sham exercises as the control activity.

Table 3 shows the data gathered from the five studies per cognitive outcome: three studies provided data on dementia onset, only one on MCI onset, and two on clinically meaningful cognitive decline; all five studies provided data for the analysis of all outcome measures combined.

Dementia Onset

Three studies (29–31) had data on dementia onset and were entered in the meta-analysis. The incidence of dementia was 3.7% (n = 949) for exercisers and 6.1% (n = 1,017) for controls. As displayed in Figure 1A, exercise was not found to reduce the risk of dementia onset: RR = 0.56; 95% CI = 0.23, 1.36; p = .20. Heterogeneity was high (I^2 = 63.1%), but there was no evidence of small-study effects (Egger's test: p = .36). The funnel plot (Supplementary Figure S2) shows a lack of studies with small standard errors (SE; in overall, larger studies of better quality) favoring the exercise group as well as a lack of studies with larger SE favoring controls. Adding data from Muscari et al. (19) (Supplementary Figure S3) provided a trend toward a positive effect of exercise against dementia onset (RR = 0.57; 95% CI = 0.30, 1.10; p = .097), with less heterogeneity (I^2 = 46.8%) and no evidence of small-study effects (Egger's test: p = .14). Since the I^2 of this latter analysis was less than 50%, we performed a fixed effects meta-analysis: a significant effect of exercise in reducing the risk of dementia onset was found, with RR = 0.65; 95% CI = 0.44, 0.97; p = .03 (Supplementary Figure S4).

MCI Onset

Only the LIFE study (31) has investigated the onset of MCI. The incidence of MCI was 10.2% (n = 686) for exercisers and 9.1% (n = 682) for controls. No effects (RR: 1.12; 95% CI = 0.81, 1.55; p = .49) of exercise compared to controls was found (Supplementary Figure S5).

Clinically Meaningful Cognitive Decline

Two studies (19,32) provided data on clinically meaningful cognitive decline. The incidence of this outcome was 14.5% (n = 124) for exercisers and 15.4% (n = 123) for controls. No effects of exercise (Supplementary Figure S6) in preventing cognitive decline was found (RR = 0.90; 95% CI = 0.42, 1.95; p = .79); heterogeneity was low (I^2 = 30.4%). Sensitivity analysis using fixed effects meta-analysis (Supplementary Figure S7) provided similar results (RR = 0.93; 95% CI = 0.51, 1.68; p = .80).

All Outcomes Combined

Only the study by Sink et al. (31) has provided data on more than one outcome of this review: dementia onset and MCI onset. Therefore, we extracted from Sink et al.'s study the combined data on dementia and MCI onset and used this data in the meta-analysis. The incidence of all cognitive outcomes combined was 11.4% (n = 1,073) for exercisers and 12.5% (n = 1,140) for controls. We did not find any benefit of exercise compared to controls (RR = 0.74; 95% CI = 0.43, 1.26; p = .27) for reducing the risk of any cognitive decline, as shown in Figure 1B; heterogeneity was substantial (I^2 = 57.1%), but there was no evidence of small-study effects (Egger's test: p = .14). As for the outcome "dementia onset", the funnel plot (Supplementary

Table 1. Characteristics of the Included Studies

Authors and Year	Country	Study Design, Participants, Groups, and Sample Size	Setting	Intervention Length (months)	Outcomes Assessed	Outcomes' Definition
Lam et al. 2012 (30)	Hong Kong	Cluster RCT. Study population (77.7 y old, 76.3% women, 3.3 y of education, MMSE was 24.5) was composed of MCI defined as: (i) CDR of 0.5; or (ii) neuropsychological criteria for amnestic-MCI with subjective cognitive complaints; objective memory impairment with reference to delayed recall of list learning test ≥ 1.5 *SD* below education- and age-matched subjects with CDR 0. Two study groups: exercise (n = 171) and controls (n = 218)	Community-dwellers and institutionalized[a]	12	Dementia	Dementia defined by DSM-IV criteria
Lam et al. 2015 (29)	Hong Kong	Cluster RCT. Study population (75.4 y old, 78.2% women, 3.9 y of education, MMSE was 25.6) was composed of MCI according with: presence of subjective cognitive complaints, and objective impairments in cognitive function: (1) impairment in episodic memory ≥1.5 *SD* below education- and age-matched normal subjects; (ii) impairment in category verbal fluency test, attention span (ie, non-memory cognitive domains) ≥1 *SD* below matched norms from epidemiological sample. Four study groups: social (n = 131), cognitive (n = 145), physical (n = 147), and cognitive + physical (n = 132). The groups social and physical were used in this review and meta-analysis as controls and exercise, respectively.	Community-dwellers[b]	12	Dementia	Unclear ("Eighteen participants (…) progressed to dementia at 1 y")
Muscari et al. 2010 (19)	Italy	Parallel-group RCT. Participants were aged 65–74 y (69.2 y old, 48.3% women, 6.5 y of education) were identified as having no previous cardiovascular diseases and no risk factors for cardiovascular disease. All of them had a MMSE ≥ 25 (mean MMSE was 26.9). Two study groups: exercise (n = 60) and controls (n = 60).	Community-dwellers	12	Cognitive decline	Declining to a MMSE between 20 and 23 at postintervention
Sink et al. 2015 (31)	United States	Parallel-group RCT. Participants (78.9 y old, 67.1% women, around 67% with a College educational level, 3MSE score was 91.5 (0–100 scale)) were 1635 (n = 1,490 with data on dementia onset) sedentary people aged 70–89 years who were at high risk for mobility disability (SPPB score ≤ 9), but who could walk 400 m (without assistance) within 15 min. They had no diagnosis of dementia or significant cognitive impairment. Two study groups: exercise (n = 818; n = 743 with dementia data) and controls (n = 817; n = 747 with dementia data).	Community-dwellers	24	Dementia MCI	Both dementia and MCI were adjudicated by two raters blinded to group allocation according with the 2011 criteria from the National Institute on Aging and the Alzheimer's Association
van Uffelen et al. 2008 (32)	Netherlands	Parallel-group RCT. Participants (75 y old, 44.1% women, 58.2% were rated as low level of education, MMSE was 29) were MCI as defined by the Petersen criteria (40): 1-Memory complaints; 2-Objective memory impairment (10 WLT delayed recall ≤ 5 and percentage savings ≤ 100);#8232; 3-Normal general cognitive function (TICS ≥19 and MMSE ≥24); 4-Intact daily functioning; 5-Absence of dementia (TICS28 ≥ 19 and MMSE ≥ 24). Two study groups: walking (n = 86) and controls (n = 93); around half of participants in each group received vitamin B supplementation and the other half received a placebo pill.	Community-dwellers	12	Cognitive decline	Two-point decline in the MMSE

Note: CDR = Clinical dementia rating; DSM = Diagnostic and Statistical Manual of Mental Disorders; MCI = Mild cognitive impairment; MMSE = Mini-mental state examination; 3MSE = Modified Mini-Mental State Examination; RCT = Randomized controlled trial; SPPB = Short physical performance battery; TICS = Telephone interview for cognitive status; WLT = Word learning test.
[a]People living in residential homes for the elderly adults. [b]"Participants (aged 60 years or over) were recruited through social centers for elders" (29).

Table 2. Characteristics of Study Groups and Interventions

Study	Exercise Intervention Used for Comparisons	Exercise Frequency (times/week)/intensity	Exercise Compliance (%)/ Attrition Rate	Exercise Session Duration (min)	Control Group Used for Comparisons/Attrition Rate
Lam et al. 2012 (30)	Tai Chi (24-forms simplified Tai Chi). Tai Chi was performed in "regular weekly sessions" under the supervision of an instructor during 4–6 wk (induction phase) in the training center; after that period, participants received a video CD with the Tai Chi program and performed the exercises in the training center or at home until the end of the intervention (maintenance phase). The Tai Chi masters provided refresher lessons every month until the 12th month to booster adherence and ensure correct performance of posture sequence.	No less than thrice/ week / Probably moderate intensity (effective for health promotion)	Compliance—unclear[a] / Attrition: 46.2%	No less than 30 min/session	Active control group. They performed muscle stretching and light toning exercise developed by physiotherapists. The same procedures applied to the Tai Chi group were also used for the exercise control group (eg, induction and maintenance phases, video CD, refresher sessions at the same frequency). Attrition: 22.5%
Lam et al. 2015 (29)	Multicomponent training composed of: one stretching and toning exercise, one mind body exercise (eg, Tai Chi) and one aerobic exercise session (eg, static bicycle riding).	Thrice/week / Probably moderate intensity (Tai Chi and static cycling[b])	Compliance: 75% / Attrition: 22.5%	60 min/session	Active control group. They participated in social activities (eg, tea gathering, film watching). The participants were arranged to attend at least three 1-h social activity sessions per week. Compliance: 71%/Attrition: 22.9%
Muscari et al. 2010 (19)	Aerobic exercise: supervised exercises in cycle ergometer, treadmill and free-body activity.	Thrice/week / Moderate intensity (70% of maximal heart rate)	Compliance—unclear[c] / Attrition: 11.7%	60 min/session	Active control group. They received educational materials about suggestions to improve lifestyle, including individualized self-administered programs to increase physical activity. Attrition: 6.7%
Sink et al. 2015 (31)	Multicomponent training composed of: walking, strength, flexibility, and balance training.	Five to six times/week (twice/week in research facilities and 3 to 4×/ wk at home) / Moderate intensity[d]	Compliance[e]: 71% for facility-led classes / Attrition: 9.2% (no data on dementia or MCI onset)	50 min/session[f]	Active control group. Subjects attended weekly health education workshops during the first 26 wk of the intervention and at least monthly sessions thereafter. Sessions lasted 60–90 min (10 min of group discussion and interaction and 5–10 min of upper- extremity stretching and flexibility exercises) and consisted of presentations, facilitator demonstrations, guest speakers, or field trips. Attrition: 8.6% (no data on dementia or MCI onset)
van Uffelen et al. 2008 (32)	Aerobic exercise: supervised, group-based walking	Twice/week / Moderate intensity (subjective appraisal by the instructor)	Compliance: 63%[g] / Attrition: 17.5% (no data on MMSE decline at 12 months)	60 min/session	Active control group. Supervised, group-based, non-aerobic light-intensity (<3 MET) exercises: relaxation, balance, flexibility and postural exercises. Compliance: 63% [g]/Attrition: 28% (no data on MMSE decline at 12 mo)

Note: MCI = Mild cognitive impairment; MET = Metabolic equivalent tasks; MMSE = Mini-mental state examination.

[a]Although authors indicated adherence was thoroughly recorded, they did not report adherence/compliance information in the original report. [b]These exercises have metabolic equivalent tasks (MET) between ≥ 3 (which is considered as moderate or higher intensity (11)) according with the Compendium of physical activities (12). [c]Compliance was probably high since only six people had less than 50% compliance. [d]Moderate-intensity exercise as reported by the authors: eg, "The physical activity sessions progressed toward a goal of 30 min of walking at moderate intensity". [e]Accelerometer data showed participants maintained moderate to vigorous physical activity throughout the 24 mo of the study. [f]Thirty minutes of walking, 10 min of strength training, and 10 min of balance training and large muscle group flexibility exercises. [g]Authors reported that the median adherence to both exercise programs (ie, walking and active controls combined) was 63% and that adherence rates did not differ between groups.

Table 3. Outcome Measures Across Studies and Groups

Studies	Dementia Onset		MCI Onset		Clinically Meaningful Cognitive Decline		All Outcomes Combined	
	Exercise Cases/*n*	Controls Cases/*n*	Exercise Cases/*n*	Controls Cases/*n*	Exercise Cases/*n*	Controls Cases/*n*	Exercise Cases/*n*	Controls Cases/*n*
Lam et al. 2012	4/92	28/169	NA	NA	-	-	4/92	28/169
Lam et al. 2015	3/114	5/101	NA	NA	-	-	3/114	5/101
Muscari et al. 2010[a]	-	-	-	-	4/53	8/56	4/53	8/56
Sink et al. 2015[b]	28/743	29/747	70/686	62/682	-	-	98/743	91/747
van Uffelen et al. 2008	-	-	NA	NA	14/71	11/67	14/71	11/67
Total	35/949	62/1,017	70/686	62/682	18/124	19/123	123/1,073	143/1,140

Note: Data used for the quantitative analyses.

MCI = Mild cognitive impairment; NA = Not applicable.

[a]A sensitivity analysis on dementia onset was undertaken by adding Muscari et al.'s data described at "clinically meaningful cognitive decline" as "dementia onset". [b]For Sink et al., data on dementia and MCI onset were summed to compose the "All outcomes combined".

Figure S8) showed a lack of both studies with small *SE* favoring the exercise group and studies with larger *SE* favoring controls.

Considerations on Sample Size and Power Calculations

Focusing on the dementia outcome (the most important clinical outcome for both clinicians and older adults) and using the data from this meta-analysis, we found that we had 69% power (POWER command in Stata v.14 for two proportions and using the chi-squared test) to detect a significant effect if the true difference in the proportions was the observed 0.024 difference between groups in the risk of dementia (6.1% in controls and 3.7% in exercise); to detect this difference in the proportions with 80% power, a sample size of 2538 subjects (n = 1,269 per study arm) would be needed.

Discussion

This review showed that only five RCTs of exercise lasting 12 months or more investigated clinically important cognitive outcomes in older adults. Results of the meta-analyses failed to find a positive effect of long-term exercise training in reducing the risk of onset of dementia, MCI, and clinically meaningful cognitive decline, as well as all these outcomes combined. The sensitivity analysis using a fixed effect approach and adding data from Muscari et al. (19) found a significant effect of exercise for reducing the risk of dementia onset by 35%. Although this result is promising, it must be interpreted with caution since it comes from a sensitivity analysis and should not be assumed as a definitive finding; indeed, since Muscari et al. (19) have not performed dementia diagnosis, this sensitivity analysis might have introduced bias if people considered as developing dementia would be false positives. Further RCTs are still needed to provide a robust response to the hypothesis that exercise decreases the risk of incident dementia.

To the best of our knowledge, this is the first review and meta-analysis gathering data on the effects of long-term exercise training on clinically important cognitive outcomes in the elderly adults. Although we found, globally, negative results, a few considerations are important to be observed: first, we identified a very small number of RCTs of exercise lasting 12 months or longer and that collected data on the cognitive outcomes of interest for this review; this is a finding in itself since it evidences an important gap in the literature. Second, the meta-analysis lacked power to detect differences between groups in the outcomes: for example, a sample of at least 1,269 people per study group would be needed to detect a difference with 80% power between exercisers and controls in the risk of developing dementia. Third, the control groups of all five included studies received active interventions. Although the control activities were probably less effective for improving cognition than the experimental interventions (ie, exercise training), it is not excluded they have benefited the cognitive function of control participants: indeed, light PA (sham exercises were operationalized in two of the included RCTs) has already been found to be associated with a reduced risk of clinically meaningful cognitive decline in observational prospective studies (33,34) and social engagement (social interactions were promoted in group-based control activities in most included studies) is also considered a contributor for brain health (35); therefore, it is possible that benefits of exercise on cognition would be greater in magnitude if comparisons had been made against no-intervention controls. Such a hypothesis should be investigated before any conclusion is established. Fourth, due to the methodological difficulties in investigating relevant changes in cognition (large time intervals), we have had to arbitrarily set the 1-year interval as the minimum intervention length leading to clinically relevant changes in cognition; this procedure may have led to a floor effect, with very few participants reaching the outcome measures within this relatively short interval. Although a follow-up length of several years would certainly lead to a higher incidence of clinically important cognitive declines, only one RCT (31) lasted more than 1 year. Fifth, all but one (30) of the included RCTs have not been designed to respond to the outcomes of this review, and none provided information on the cost-effectiveness of the exercise intervention in the context of cognitive outcomes. The two RCTs (19,31) including people without known cognitive impairment have assessed participants' baseline cognition using a neuropsychological test. Although, in the LIFE study (31), potential cases of cognitive decline were evaluated by a panel of clinical experts in order to determine MCI and dementia, the study by Muscari et al. relied only on the MMSE cut-off < 24 as the cognitive exclusion criterion; therefore, regarding this latter

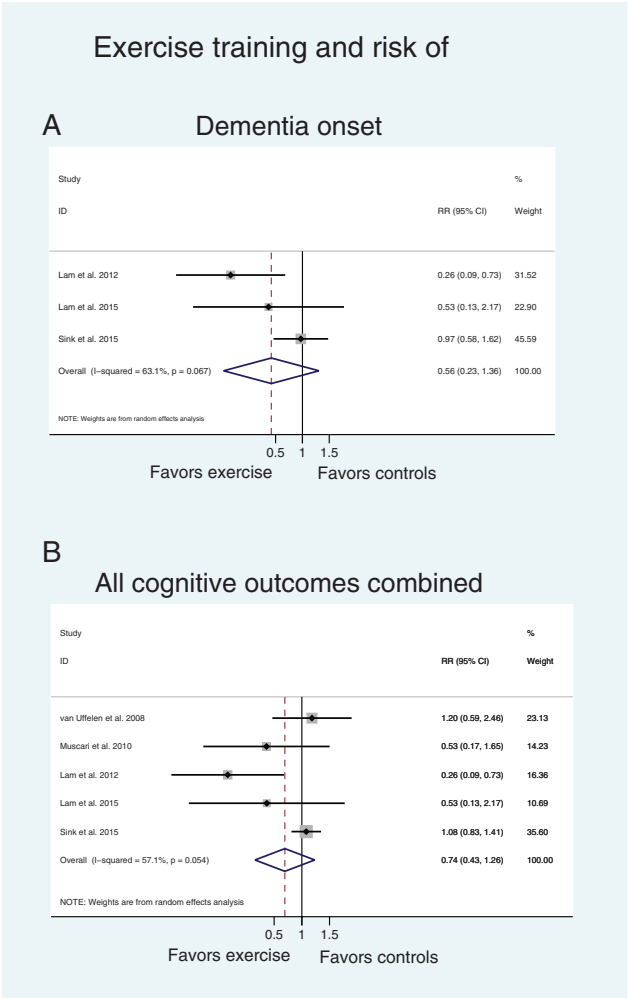

Figure 1. Meta-analysis of the effects of exercise on the risk of dementia onset (**A**) and all cognitive outcomes combined (**B**). Data on dementia onset, mild cognitive impairment onset, and other clinically meaningful cognitive decline were combined to create the variable "all cognitive outcomes combined" (part **B** of the Figure).

RCT, it is possible that some participants have already had an undiagnosed clinically relevant cognitive decline (eg, MCI) at baseline, even though participants' baseline MMSE scores were high (around 27) and similar between study groups.

This study has also strengths that are worth mentioning: the overall quality of the included studies can be considered high; of note, no significant differences between exercisers and controls have been found for cognitive function at baseline for all RCTs and all, but one RCT (29), had similar PA/exercise levels between study groups at baseline. Moreover, the protective effect of exercise against dementia onset obtained in a fixed-effect sensitivity analysis deserves to be pursued; therefore, rerunning the meta-analysis when new data from other RCTs will be available will be a crucial step to draw robust conclusions on the potential of exercise for preventing dementia onset. Another important aspect to be highlighted relates to the fact this review has proven that combining data for well-led RCTs of a behavioral intervention (ie, exercise) is feasible and may lead to informative findings (even though methodological barriers exist, such as, paucity of large-scale, long-term RCTs); indeed, due to the high costs associated with cognitive decline and dementia (36,37), providing evidence on the 1-year reduction in the incidence of this disease represents a major information with important implications from a public health perspective.

Dementia is an evolving disease that may start decades before any clinical symptom is appraised (38). For this reason, the associations of PA and exercise with dementia onset and other clinically relevant cognitive outcomes have been traditionally examined using longitudinal observational studies (1–4), with inherent limitations, particularly the impossibility of establishing causality inferences. Even though examining the preventive effects of exercise on dementia onset may be beyond the full resolution by RCTs (difficulty in conducting and maintaining high adherence to exercise interventions lasting several years), data from long-term RCTs are useful and may provide essential cause-effect information. Further well-conducted, long-term exercise RCTs are still needed. In order to establish more precise recommendations on PA and exercise, future RCTs should investigate the best exercise regimen (ie, type, frequency, intensity, and duration) for preventing clinically significant cognitive decline and if the potential cognitive benefits of exercise would be more effective in "at-risk" subgroups (eg, APOE4 carriers vs no-carriers (39)); such information might lead to tailored interventions with increased efficacy. Cost-effectiveness analysis should be carefully examined in order to promote sustained exercise programs in the current public health context characterized by limited resources. If, after the addition of future high-quality RCTs, the scientific community finds a positive effect of exercise in reducing the risk of dementia, exercise training should definitively make part of the front-line treatment for the prevention of cognitive decline and dementia.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

None reported.

Acknowledgments

The authors would like to thank Marijke Hopman-Rock and Jannique van Uffelen for providing additional data to this study.

Conflict of Interest

None reported.

Sponsor's Role

None.

References

1. Sofi F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med*. 2011;269:107–117. doi:10.1111/j.1365-2796.2010.02281.x
2. Beckett MW, Ardern CI, Rotondi MA. A meta-analysis of prospective studies on the role of physical activity and the prevention of Alzheimer's disease in older adults. *BMC Geriatr*. 2015;15:9. doi:10.1186/s12877-015-0007-2
3. Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia?: A systematic review and

meta-analysis of longitudinal studies. *BMC Public Health*. 2014;14:510. doi:10.1186/1471-2458-14-510
4. Stephen R, Hongisto K, Solomon A, Lönnroos E. Physical activity and Alzheimer's disease: a systematic review. *J Gerontol A Biol Sci Med Sci*. 2017;72:733–739. doi:10.1093/gerona/glw251
5. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol*. 2014;13:788–794. doi:10.1016/S1474-4422(14)70136-X
6. Young J, Angevaren M, Rusted J, Tabet N. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev*. 2015:(4)CD005381. doi:10.1002/14651858.CD005381.pub4
7. Kelly ME, Loughrey D, Lawlor BA, Robertson IH, Walsh C, Brennan S. The impact of exercise on the cognitive functioning of healthy older adults: a systematic review and meta-analysis. *Ageing Res Rev*. 2014;16:12–31. doi:10.1016/j.arr.2014.05.002
8. Gates N, Fiatarone Singh MA, Sachdev PS, Valenzuela M. The effect of exercise training on cognitive function in older adults with mild cognitive impairment: a meta-analysis of randomized controlled trials. *Am J Geriatr Psychiatry*. 2013;21:1086–1097. doi:10.1016/j.jagp.2013.02.018
9. Zheng G, Xia R, Zhou W, Tao J, Chen L. Aerobic exercise ameliorates cognitive function in older adults with mild cognitive impairment: a systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med*. 2016;50:1443–1450. doi:10.1136/bjsports-2015–095699
10. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
11. Haskell WL, Lee IM, Pate RR, et al.; American College of Sports Medicine; American Heart Association. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116:1081–1093. doi:10.1161/CIRCULATIONAHA.107.185649
12. Ainsworth BE, Haskell WL, Herrmann SD, et al. The Compendium of Physical Activities Tracking Guide. [Internet]. Cited May 5, 2017. Available from: https://sites.google.com/site/compendiumofphysicalactivities/
13. 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;12:189–198.
14. Hensel A, Angermeyer MC, Riedel-Heller SG. Measuring cognitive change in older adults: reliable change indices for the Mini-Mental State Examination. *J Neurol Neurosurg Psychiatry*. 2007;78:1298–1303. doi:10.1136/jnnp.2006.109074
15. Tombaugh TN. Test-retest reliable coefficients and 5-year change scores for the MMSE and 3MS. *Arch Clin Neuropsychol*. 2005;20:485–503. doi:10.1016/j.acn.2004.11.004
16. Higgins JP, Altman DG, Gøtzsche PC, et al.; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi:10.1136/bmj.d5928
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560. doi:10.1136/bmj.327.7414.557
19. Muscari A, Giannoni C, Pierpaoli L, et al. Chronic endurance exercise training prevents aging-related cognitive decline in healthy older adults: a randomized controlled trial. *Int J Geriatr Psychiatry*. 2010;25:1055–1064. doi:10.1002/gps.2462
20. Bartos A, Raisova M. The Mini-Mental State Examination: Czech norms and cutoffs for mild dementia and mild cognitive impairment due to Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2016;42:50–57. doi:10.1159/000446426
21. Boban M, Malojčić B, Mimica N, et al. The reliability and validity of the mini-mental state examination in the elderly Croatian population. *Dement Geriatr Cogn Disord*. 2012;33:385–392. doi:10.1159/000339596
22. Kahle-Wrobleski K, Corrada MM, Li B, Kawas CH. Sensitivity and specificity of the mini-mental state examination for identifying dementia in the oldest-old: the 90+ study. *J Am Geriatr Soc*. 2007;55:284–289. doi:10.1111/j.1532-5415.2007.01049.x
23. Perneczky R, Wagenpfeil S, Komossa K, Grimmer T, Diehl J, Kurz A. Mapping scores onto stages: mini-mental state examination and clinical dementia rating. *Am J Geriatr Psychiatry*. 2006;14:139–144. doi:10.1097/01.JGP.0000192478.82189.a8
24. Tsoi KKF, Chan JYC, Hirai HW, Wong SYS, Kwok TCY. Cognitive tests to detect dementia: a systematic review and meta-analysis. *JAMA Intern Med*. 2015;175:1450–1458. doi:10.1001/jamainternmed.2015.2152
25. Chapman KR, Bing-Canar H, Alosco ML, et al. Mini Mental State Examination and Logical Memory scores for entry into Alzheimer's disease trials. *Alzheimers Res Ther*. 2016;8:9. doi:10.1186/s13195-016-0176-z
26. Health Services Research Unit. University of Aberdeen. Database of ICCs:Spreadsheet (Empirical estimates of ICCs from changing professional practice studies) [Internet]. Cited October 29, 2013. Available from: http://www.abdn.ac.uk/hsru/research/research-tools/study-design
27. Elley CR, Kerse N, Chondros P, Robinson E. Intraclass correlation coefficients from three cluster randomised controlled trials in primary and residential health care. *Aust N Z J Public Health*. 2005;29:461–467.
28. Ukoumunne OC, Gulliford MC, Chinn S, Sterne JA, Burney PG. Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review. *Health Technol Assess*. 1999;3:iii–i92.
29. Lam LC-W, Chan WC, Leung T, Fung AW-T, Leung EM-F. Would older adults with mild cognitive impairment adhere to and benefit from a structured lifestyle activity intervention to enhance cognition?: A cluster randomized controlled trial. *PloS One*. 2015;10:e0118173. doi:10.1371/journal.pone.0118173
30. Lam LCW, Chau RCM, Wong BML, et al. A 1-year randomized controlled trial comparing mind body exercise (Tai Chi) with stretching and toning exercise on cognitive function in older Chinese adults at risk of cognitive decline. *J Am Med Dir Assoc*. 2012;13:568.e15–20. doi:10.1016/j.jamda.2012.03.008
31. Sink KM, Espeland MA, Castro CM, et al.; LIFE Study Investigators. Effect of a 24-month physical activity intervention vs health education on cognitive outcomes in sedentary older adults: the LIFE Randomized Trial. *JAMA*. 2015;314:781–790. doi:10.1001/jama.2015.9617
32. van Uffelen JGZ, Chinapaw MJM, van Mechelen W, Hopman-Rock M. Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. *Br J Sports Med*. 2008;42:344–51. doi:10.1136/bjsm.2007.044735
33. Krell-Roesch J, Pink A, Roberts RO, et al. Timing of physical activity, apolipoprotein E ε4 genotype, and risk of incident mild cognitive impairment. *J Am Geriatr Soc*. 2016;64:2479–2486. doi:10.1111/jgs.14402
34. Lee S, Yuki A, Nishita Y, et al. Research relationship between light-intensity physical activity and cognitive function in a community-dwelling elderly population-an 8-year longitudinal study. *J Am Geriatr Soc*. 2013;61:452–453. doi:10.1111/jgs.12119
35. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. *Alzheimers Dement J Alzheimers Assoc*. 2016;12:459–509.
36. Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. *N Engl J Med*. 2013;368:1326–1334. doi:10.1056/NEJMsa1204629
37. Prince M, Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina M. *World Alzheimer Report 2015: The Global Impact of Dementia [Internet]*. Alzheimer's Disease International, London; 2015. Available from: https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf. Accessed April 11, 2017.
38. Jack CR Jr, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol*. 2013;12:207–216. doi:10.1016/S1474-4422(12)70291-0
39. Tan ZS, Spartano NL, Beiser AS, DeCarli C, Auerbach SH, Vasan RS, et al. Physical activity, brain volume, and dementia risk: The Framingham Study. *J Gerontol A Biol Sci Med Sci*. 2017;72:789–95. doi:10.1093/gerona/glw130
40. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56:303–308.