JAMDA 21 (2020) 1415–1422

JAMDA

journal homepage: www.jamda.com

Review Article

Physical Activity and Exercise in Mild Cognitive Impairment and Dementia: An Umbrella Review of Intervention and Observational Studies

Jacopo Demurtas MD [a,b], Daniel Schoene PhD [c,d], Gabriel Torbahn MPH [e], Alessandra Marengoni MD, PhD [f], Giulia Grande MD [g], Liye Zou PhD [h], Mirko Petrovic MD, PhD [i], Stefania Maggi MD, PhD [j], Matteo Cesari MD, PhD [k], Sarah Lamb MD [l], Pinar Soysal MD [m], Wolfgang Kemmler PhD [n], Cornel Sieber MD [e], Christoph Mueller MD [o], Susan D. Shenkin MD [p], Lukas Schwingshackl MD [q], Lee Smith PhD [r], Nicola Veronese MD [s,t,*], on behalf of The European Society of Geriatric Medicine Special Interest Group in Systematic Reviews and Meta-Analyses, Frailty, Sarcopenia, and Dementia

[a] *Primary Care Department Azienda USL Toscana Sud Est, Grosseto, Italy*
[b] *Clinical and Experimental Medicine PhD Program, University of Modena and Reggio Emilia, Modena, Italy*
[c] *Institute of Medical Physics, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany*
[d] *Department of Geriatric Rehabilitation, Robert-Bosch Hospital, Stuttgart, Germany*
[e] *Institute for Biomedicine of Aging, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nürnberg, Germany*
[f] *Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy*
[g] *Department of Neurobiology, Care Sciences and Society, Aging Research Center, Karolinska Institutet and Stockholm University, Stockholm, Sweden*
[h] *Exercise and Mental Health Laboratory, Shenzhen University, Shenzhen, China*
[i] *Section of Geriatrics, Department of Internal Medicine and Paediatrics, Ghent University, Ghent, Belgium*
[j] *National Research Council, Neuroscience Institute - Aging Branch, Padova, Italy*
[k] *Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy*
[l] *Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford University, Oxford, United Kingdom*
[m] *Faculty of Medicine, Department of Geriatric Medicine, Bezmialem Vakif University, Istanbul, Turkey*
[n] *Institute of Medical Physics, Friedrich-Alexander University Erlangen-Nürnberg, Nuremberg, Germany*
[o] *King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, UK*
[p] *Geriatric Medicine, Usher Institute, University of Edinburgh, Edinburgh, UK*
[q] *Faculty of Medicine, Institute for Evidence in Medicine, Medical Center-University of Freiburg, University of Freiburg, Freiburg, Germany*
[r] *The Cambridge Centre for Sport and Exercise Science, Anglia Ruskin University, Cambridge, UK*
[s] *Unità Locale Socio Sanitaria 3 "Serenissima", Primary care Department, Venice, Italy*
[t] *Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, Palermo, Italy*

Keywords:
Physical activity
physical exercise
dementia
mild cognitive impairment
cognition
umbrella review

A B S T R A C T

Objectives: The aim of this umbrella review was to determine the effect of physical activity/exercise on improving cognitive and noncognitive outcomes in people with MCI (mild cognitive impairment) and dementia.
Design: Umbrella review of systematic reviews (SR), with or without meta-analyses (MAs), of randomized controlled trials (RCTs) and observational studies.
Settings and Participants: People with MCI or dementia, confirmed through validated assessment measures. Any form of physical activity/exercise was included. As controls, we included participants not following any prespecified physical activity/exercise intervention or following the same standard protocol with the intervention group.

* Address correspondence to Nicola Veronese, MD, Azienda ULSS 3 (Unità Locale Socio Sanitaria) "Serenissima", Primary Care Department, Dolo-Mirano District, Venice, Italy.
E-mail address: ilmannato@gmail.com (N. Veronese).

https://doi.org/10.1016/j.jamda.2020.08.031

Methods: The protocol was registered in PROSPERO (CDR 164197). Major databases were searched until December 31, 2019. The certainty of evidence of statistically significant outcomes was evaluated using the Grading of Recommendations Assessment, Development and Evaluation approach. SRs' findings, without a formal MA, were reported descriptively.
Results: Among 1160 articles initially evaluated, 27 SRs (all of RCTs, 9 without MA) for a total of 28,205 participants with MCI/dementia were included. In patients with MCI, mind-body intervention (standardized mean difference [SMD] = 0.36; 95% confidence intervals [CI] 0.20–0.52; low certainty) and mixed physical activity interventions (SMD = 0.30; 95% CI 0.11–0.49; moderate certainty) had a small effect on global cognition, whereas resistance training (SMD = 0.80; 95% CI 0.29–1.31; very low certainty) had a large effect on global cognition. In people affected by dementia, physical activity/exercise was effective in improving global cognition in Alzheimer disease (SMD = 1.10; 95% CI 0.65–1.64; very low certainty) and in all types of dementia (SMD = 0.48; 95% CI 0.22–0.74; low certainty). Finally, physical activity/exercise improved noncognitive outcomes in people with dementia including falls, and neuropsychiatric symptoms.
Conclusions and Implications: Supported by very low-to-moderate certainty of evidence, physical activity/exercise has a positive effect on several cognitive and noncognitive outcomes in people with MCI and dementia, but RCTs, with low risk of bias/confounding, are still needed to confirm these relationships.

The number of people living with dementia worldwide in 2015 was estimated at 47.5 million, reaching 75.6 million in 2030.[1] Future projections are indicating that this number will be 135.46 million in 2050.[1] Approximately 7.7 million new cases of dementia are anticipated each year.[1] It is widely known that people affected by mild cognitive impairment (MCI) are at greater risk of dementia than the general population, and the annual progression rates range from 10% to 15%.[2,3]

Unfortunately, there are no curative treatments for dementia or MCI and so epidemiological research regarding risk factors for this disease is of importance. It has been estimated that 3% of dementia cases could be prevented by increasing levels of free-living physical activity[4,5] and a growing body of literature is reporting the importance of physical activity and exercise for preventing and eventually slowing down the pathological process and dementia-related problems.[6]

In this regard, older people who are physically active are more likely to maintain cognition than those who are not.[4] In a meta-analysis including 15 prospective cohort studies and 33,816 individuals without dementia at baseline, greater physical activity levels were associated with a significant reduction in the onset of dementia, with high levels of physical activity being the most protective.[7] In people already affected by dementia, the important role of physical activity was confirmed; exercise was found to help in improving important outcomes, such as cognition.[8] Moreover, physical activity in general and exercise interventions in particular might help in ameliorating behavioral and psychological symptoms in dementia (BPSD).[9] However, results are not consistent: a recent large trial has, for example, reported that after a moderate-to-high intensity multicomponent exercise program in people with dementia, intervention group participants performed worse in some cognitive aspects.[10]

The effect of physical activity/exercise in MCI is still not clear. Some studies have reported that physical activity/exercise can prevent the transition from MCI to dementia and that these interventions can improve some cognitive and noncognitive outcomes in this specific population at higher risk for dementia.[11]

Given the above, the aim of this umbrella review, promoted by the European Geriatric Medicine Society, is to understand the effect of physical activity/exercise on improving cognitive and noncognitive outcomes in people with MCI/dementia.

Materials and Methods

The protocol for this umbrella review is available at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=164197.

Literature Search and Inclusion Criteria

We searched electronic databases MEDLINE/Ovid, PsychINFO, CINHAL, Embase, and Cochrane database for Systematic Reviews from inception to December 31, 2019. We used a combination of MeSH-terms, text words (in title/abstract and keywords) of dementia, MCI, physical activity, and exercise. Full details of the search strategy for MEDLINE/Ovid is reported in Supplementary Table 1. Also, we checked the reference lists of all eligible articles and other relevant narrative articles for possible inclusion.

Two reviewers (GG, NV) independently searched titles/abstracts for eligibility using https://www.covidence.org/. Any disagreement between reviewers was resolved through discussion and a final agreement was reached. Four authors (NV, DS, JD, PS), in couples, assessed the full-text of those articles retained after the title/abstract screening. Disagreements between reviewers were resolved through discussion and a final agreement was reached.

We included the following:

(1) systematic reviews [SRs] with or without meta-analyses [MAs] of interventions of only randomized controlled trials (RCTs) regarding physical activity/exercise interventions in people with MCI;
(2) SRs with or without MAs of observational (prospective and case-control) studies comparing people with low physical activity level (versus high level) for the development of dementia in people already affected by MCI;
(3) SRs with or without MAs of interventions of only RCTs regarding physical activity/exercise interventions in people affected by dementia. We included any form of physical activity (ie, any movement that is carried out by the skeletal muscles that requires energy), as defined by authors. For exercise (ie, a planned, structured, repetitive and intentional movement intended to improve or maintain physical fitness), we included aerobic exercise, resistance exercise, balance and coordination exercise, motor-cognitive interventions (Virtual Reality, Exergaming), mixed programs (eg, aerobic and resistance exercise together), physiotherapy, and physical activity during occupational therapy. As controls, we included participants not following any prespecified physical activity/exercise intervention or following the same standard protocol with the intervention group additionally receiving an exercise/physical activity component.

When more than 1 SR/MA assessed the same outcome in the same population, we only included the one with the larger number of studies.

Outcomes

Primary outcomes: cognitive function explored with validated tests (such as the Mini-Mental State Examination, MMSE[12]) and categorized according to global and specific domains (attention, executive function, memory, motor speed, and language);

Secondary outcomes:
(1) incidence of dementia in people with MCI, in observational studies;
(2) BPSDs, measured with validated tests such as the neuropsychiatric inventory (NPI)[13];
(3) adverse events (eg, mortality, falls, fractures, hospitalizations, nursing home admissions);
(4) medical events (eg, stroke);
(5) health-related quality of life;
(6) functional performance tests (eg, gait speed, chair rise, balance, Short Physical Performance Battery [SPPB], aerobic capacity, strength).

Data Extraction

Data extraction was led by 2 independent reviewers (JD, GG) and disagreements were resolved through consensus with the senior author (NV). This task proceeded with a 2-step approach. In the first level reported effect sizes (ESs) and the number of studies included in the SR/MA was extracted; in the second level abstraction, this data was confirmed at the single study level.

We extracted the following data from included studies: the number of studies included, the number of participants in each arm, participant demographics, the length of follow-up, details of physical activity/exercise intervention (type, duration, intensity, frequency), ES of outcomes of interest, heterogeneity, publication bias, conflict of interest.

Next, the study-specific estimated relative risk for health outcomes was extracted (risk ratio, [RR], odds ratio [OR], hazard ratio [HR], incident risk ratio [IRR], [standardized] mean difference [(S)MD]), along with the 95% confidence interval (CI), and the number of participants for each study by randomization, divided in active intervention and controls. The SMD is used as a summary statistic in meta-analysis when the studies all assess the same outcome using a variety of ways (eg, all studies measure disability, but they use different scales for measuring this characteristic). In this regard, it is necessary to standardize the results of the studies to a uniform scale before combining them.[14] The MD is a standard statistic that measures the absolute difference between the mean value between 2 groups and it is commonly used as an effect size when outcome measurements in all studies are made on the same scale.[14]

Risk of Bias Assessment

Two reviewers (JD, PS) assessed the risk of bias of the included SRs and MAs using ROBIS (Risk of Bias Assessment Tool for Systematic Reviews). The disagreements were resolved by third reviewer (LS). ROBIS includes 4 different domains: domain 1, study eligibility criteria; domain 2, identification and selection of studies; domain 3, data collection and study appraisal; domain 4, synthesis and findings.

Data Synthesis and Analysis

For each meta-analysis, we estimated the summary effect size and its 95% CI by using a random-effects model, with the DerSimonian-Laird's method.[15] Between-study inconsistency was estimated with the I^2 metric, with values $\geq$50% indicative of high heterogeneity.[16] All statistical analyses were conducted in Stata, version 14.0 (StataCorp, College Station, TX).

Evidence from meta-analyses of RCTs was assessed in terms of the significance of the summary effect. In case of statistically significant outcomes, we evaluated the evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) assessment, that takes in account several important domains in the certainty of the evidence, including study design, risk of bias, inconsistency, indirectness, imprecision and other aspects, such as publication bias.[17] The GRADE assessment was made by an investigator (JD) and checked and corrected, if needed, by another reviewer (NV). Supplementary Table 2 reports the criteria used, for each domain, for doing the GRADE, as agreed a priori by 4 investigators (JD, LS, NV, GT). The certainty of the evidence was then reported as: very low (the true effect is probably markedly different from the estimated effect), low (the true effect might be markedly different from the estimated effect), moderate (the true effect is probably close to the estimated effect), or high (there is a lot of confidence that the true effect is similar to the estimated effect).[17]

Results

Literature Search

As shown in Supplementary Figure 1, 1160 articles were initially included. Of them, 159 full texts were retrieved, with 27 articles finally included (18 MAs and 9 SRs without MA) (reference list in Supplementary Table 3). No observational study on physical activity/exercise in MCI for preventing dementia was included, leaving only RCTs for this umbrella review.

Descriptive Findings of the Meta-Analyses Included

Table 1 reports the descriptive findings of the SRs included. Overall, a total of 28,205 participants with MCI/dementia were included, with 14,209 randomized to physical activity/exercise intervention and 13,886 to controls. The physical activity/exercise interventions greatly varied in terms of type, frequency, duration, and intensity across the included SRs, which are fully reported in Table 1. Of importance, in several SRs, poor details regarding the type and the modality of physical activity/exercise were reported.

Mild Cognitive Impairment

Table 1 and Supplementary Table 4 summarize the main findings regarding physical activity/exercise on cognitive function in people affected by MCI. Physical activity/exercise significantly improved global cognition, since mind-body intervention had a small effect on global cognition (SMD = 0.36; 95% CI 0.20–0.52; low certainty according to the GRADE), such as mixed physical activity interventions (SMD = 0.30; 95% CI 0.11–0.49; moderate certainty) and resistance training had a large effect on global cognition (SMD = 0.80; 95% CI 0.29–1.31; very low certainty of evidence). In people with MCI, physical activity/exercise had beneficial effects on attention (SMD = 0.39), executive function (SMD = 0.42), and memory (SMD = 0.26) with a certainty of evidence varying from low to moderate, as fully reported in Table 2 and Supplementary Table 4.

Finally, in people with MCI, as shown in Table 3 that reports the findings of narrative reviews, mixed physical activity/exercise intervention and aerobic exercise improved physical function and cognitive outcomes, but no effect on disability was observed.

Table 1
Descriptive Findings of the Studies Included

Author of the Review	Year	Type of Review	Total Sample Size	Randomized to Physical Activity/Exercise	Randomized to Control Group	Physical Activity/Exercise Description (Type, Frequency, Duration, Intensity) Intervention	Outcome Measures
Adamson	2015	MA	1324	662	662	Physical activity mixed. Mean frequency 3 times per wk; Mean duration 40 min.	Depression
Almeida	2019	MA	1129	637	492	Home-based physical activity. No details regarding mean frequency. duration. intensity	The Mini-Mental Status Examination, Neuropsychiatric Inventory, Alzheimer's Disease Cooperative Study Group ADL scale, Functional Reach test, Timed Up and Go test in people with dementia.
Barreto	2015	MA	1627	622	965	Physical activity mixed- Mean frequency 3.38 times per wk; Mean duration 38 min.	Global BPSD; Mortality
Brown	2019	MA	524	226	228	Home-based physical activity. No details regarding mean frequency. duration. intensity	Disability and Mobility in Alzheimer Disease
Burge	2012	MA	278	126	152	Physical activity mixed- Mean frequency 2.8 times per wk; Mean duration 36.6 min.	Disability in moderate severe dementia
Burton	2015	MA	336	157	179	Physical activity mixed. No details regarding mean frequency. duration. Intensity.	Falls and mean number of falls in dementia
Cummisuli	2017	MA	768	384	384	Aerobic exercise. Mean frequency 2.55 times per wk; Mean duration 57 min.	Cognitive function in MCI
Cummisuli	2018	MA	554	277	277	Aerobic exercise. Mean frequency 2.57 times per wk; Mean duration 46.25 min.	Cognitive function in Alzheimer disease
Fleiner	2017	MA	201	130	71	Physical activity mixed- Mean frequency 3 times per wk; Mean duration 56 min.	BPSD in dementia
Gates	2013	MA	1695	860	835	Physical activity mixed. Mean frequency 3 times per wk; Mean duration 40 min.	TMTB; Digital symbol substitution test; Digit span
Groot	2016	MA	802	433	369	Physical activity mixed; Mean duration 146 min.	Cognitive function in dementia
Jia	2019	MA	673	342	331	Physical activity mixed; Mean frequency 1.8 times per wk; Mean duration 40 min.	Cognitive function in Alzheimer disease
Leng	2018	MA	2289	1270	1019	Physical activity mixed. No details regarding mean frequency. duration. intensity	Depressive symptoms, BPSD, anxiety, apathy
Lewis	2017	MA	945	306	639	Home-based physical activity. No details regarding mean frequency. duration. intensity	Physical performance test, falls and hospital readmissions
Li	2019	MA	2051	1217	834	Physical activity mixed. No details regarding mean frequency. duration. intensity	Disability (ADL) in dementia
Lim	2019	MA	325	166	159	Tai Chi. Mean frequency 3 times per wk; Mean duration 46 min.	Global cognitive function; Specific cognition
Ojagbemi	2019	MA	765	385	380	Physical activity mixed- Mean frequency 1 time per wk; Mean duration 130 min.	Quality of life
Packer	2019	MA	3380	1698	1682	Physical activity mixed- Mean frequency 1.66 times per wk; Mean duration 120 min.	Hospitalization; Length of stay in hospital
Song	2018	MA	929	500	429	Physical activity mixed- Mean frequency 2.45 times per wk; Mean duration 54.5 min.	Global cognition; Immediate recall; Delayed memory; Fluency; Stroop
Wang	2019	MA	1088	549	539	Resistance training; Mean frequency 2.5 times per wk; Mean duration 63 min.	Cognitive function in MCI
Zheng	2016	MA	1587	773	814	Aerobic exercise. Mean frequency 2.28 times per wk; Mean duration 53 min.	Immediate recall; Delayed memory in MCI; Attention; Executive function; Fluency
Zou	2019	MA	940	392	548	Mind-body exercises. Mean frequency 3.8 times per wk; Mean duration 60 min.	Cognitive function; Processing speed; Attention; STM; Executive function; Visuospatial executive function
Bruderer-Hofstetter	2018	MA	1770	885	885	Physical activity mixed. No details regarding mean frequency. duration. intensity	Disability in IADL; physical function tests
Blankevoort	2010	SR	642	385	257	Physical activity mixed. No details regarding mean frequency. duration. intensity	Strength, balance, mobility and ADL performance
Brett	2016	SR	901	498	403	Physical activity mixed. No details regarding mean frequency. duration. intensity	Health and wellbeing in dementia in nursing homes
Guitar	2018	SR	259	127	132	Physical activity mixed- Mean frequency 2.5 times per wk; Mean duration 129 min.	Executive function
Learner	2016	SR	423	202	221	Physical activity mixed- Mean frequency 3, 4 times per wk; Mean duration 37.5 min.	Cognitive function in dementia in nursing homes
Total			28,205	14,209	13,886		

ADL, Activities of Daily Living; BPSD, Behavioral and Psychological Symptoms in Dementia; IADL, Instrumental activities of daily living; MA, Meta-Analyses; MCI, Mild Cognitive Impairment; SR, Systematic Reviews; STM, Short-term memory; TMTB, Trail Making Test.

Table 2
Summary of the Main Findings Regarding Cognitive Function of the Meta-analyses Included in the Umbrella Review

	Global Cognition	Attention	Executive Function	Memory	Motor Speed	Language
MCI	*Mind-body intervention* Small effect Low certainty *Mixed physical activity intervention* Small effect Moderate certainty *Resistance training intervention* Large effect Very low certainty	*Mind-body intervention for visuospatial executive function* Small effect Low certainty *Mind-body intervention* Small effect Low certainty	*Mind-body intervention* Small effect Low certainty	*Mind-body intervention* Medium effect Low certainty *Tai Chi intervention* Medium effect Low certainty *Aerobic exercise intervention for delayed memory* Small effect Moderate certainty	No statistically significant effect	No statistically significant effect
Dementia	*Mixed physical activity intervention in AD* Large effect Very low certainty *Mixed physical activity intervention in all dementias* Medium effect Low certainty	No statistically significant effect	No statistically significant effect	No statistically significant effect	No statistically significant effect	No statistically significant effect

AD, Alzheimer's disease.

Table 3
Summary of Findings of the Systematic Reviews (Without Meta-analysis) Included

Author, Year	Intervention	Population	Outcome	Number of Studies	Main Findings
Cammisuli, 2017	Aerobic exercise	AD	Cognitive function	8	There is scarce evidence that aerobic exercise improves cognition in AD patients. Overall, the included studies reported only positive effects for patients' global cognition after intervention, mainly due to a lack of accurate neuropsychological assessment of each cognitive domain
Guitar, 2018	PA mixed	AD	Executive function	4	Significant improvement was seen in all studies.
Almeida, 2019	PA home based	Dementia	BPSD	7	Small effect on BPSD (ES = −0.37, 95% CI −0.57, −0.017)
Almeida, 2019	PA home based	Dementia	Carer's burden	3	Medium reduction on carer's burden (ES = −0.63, 95% CI −0.94, −0.32) for NPI Caregivers subscale and low and negative (ES = −0.45, 95% CI −0.77, −0.13) for ZBI
Almeida, 2019	PA home based	Dementia	Cognitive function	6	Medium effect on MMSE (ES = 0.71, 95% CI 0.43, 0.99)
Almeida, 2019	PA home based	Dementia	Disability	4	Important effect on disability (ES = 0.80, 95% CI 0.53, 1.07)
Almeida, 2019	PA home based	Dementia	Health-related physical fitness	6	Large effect on physical tests Functional Reach test (ES = 2.24, 95% CI 1.80, 2.68), TUG test (ES = −2.40, 95% CI −2.84, −1.96)
Almeida, 2019	PA home based	Dementia	QoL	2	Small effect on QoL
Blankevoort, 2010	PA mixed	Dementia	Physical performance test	10	Lower-limb strength improved equally in multicomponent interventions and progressive resistance training.
Fleiner, 2017	PA mixed	Dementia	BPSD	3	All 3 RCTs reported significant reductions of BPSD and differences in comparison to the pre-test and control groups.
Brown, 2019	PA home based	Dementia home	Disability	7	Significant effect of physical activity on functional ability, particularly on mobility items
Brown, 2019	PA home based	Dementia home	Mobility	7	Significant effect of physical activity on functional ability, particularly on mobility items
Brett, 2016	PA mixed	Dementia nursing home	Cognitive function	7	Among 7 RCTs initially included, physical activity improved cognitive measures in two
Brett, 2016	PA mixed	Dementia nursing home	Mood and Depression	5	Not clear effect on depression and mood measures
Brett, 2016	PA mixed	Dementia nursing home	Functional ability	5	Significant effect of physical activity on functional ability, particularly on mobility items
Brett, 2016	PA mixed	Dementia nursing home	Mobility	5	Significant effect of physical activity on functional ability, particularly on mobility items
Learner, 2016	PA mixed	Dementia nursing home	Cognitive function	5	There is moderate-to-strong evidence that physical activity can effectively maintain cognitive function in nursing home residents with Dementia
Burge	PA mixed	Moderate severe dementia	Disability	5	In 1 high-quality study over 5, physical activity programs significantly delayed deterioration of ADL performance.
Bruderer-Hofstetter, 2018	PA mixed	MCI	Disability	3	In none of the studies, MCT was superior to active comparison or control interventions on IADL performance.
Bruderer-Hofstetter, 2018	PA mixed	MCI	Physical performance test	4	All 3 RCTs reported significant effect of physical activity on balance and physical tests
Cammisuli, 2017	Aerobic exercise	MCI	Cognitive function	9	There is evidence that aerobic exercise improves cognition in MCI patients. Overall research reported moderate effects for global cognition, logical memory, inhibitory control and divided attention

AD, Alzheimer's disease; ADL, Activities of Daily Living; BPSD, Behavioral and Psychological Symptoms in Dementia; IADL, Instrumental Activities of Daily Living; ES, Effect Size; MCT, Multicomponent interventions; MMSE, Mini-Mental State Examination; NPI, neuropsychiatric inventory; PA, physical activity; QoL, Quality of Life; TUG, Timed Up and Go; ZBI, Zarit Burden Interview.

Dementia

As reported in Table 2 and Supplementary Table 4, in people affected by dementia, mixed physical activity/exercise was effective in improving global cognition in Alzheimer disease (SMD = 1.10; 95% CI 0.65–1.64; very low certainty) and in all types of dementia (SMD = 0.48; 95% CI 0.22–0.74; low certainty), whilst no effect of physical activity/exercise on attention, executive function, memory, motor speed, and language was observed.

Table 4 summarizes the findings of physical activity/exercise on noncognitive outcomes in people affected by dementia, since no outcome included people with MCI. Home-based physical activity interventions significantly improved disability (SMD = 0.77; 95% CI 0.17–1.37; low certainty of evidence), depressive symptoms (depressive symptoms: SMD = −0.18; 95% CI −0.33 to −0.02; moderate certainty of evidence) and BPSD (MD = −4.62; 95% CI −9.08 to −0.16; very low certainty of evidence). Moreover, physical activity/exercise interventions significantly decreased the risk of falls and the number of falls (MD = −1.06; 95% CI −1.67 to −0.46), with a certainty of evidence low/moderate (Table 4).

As reported in Table 3, in 2 SRs without meta-analysis involving participants with Alzheimer's disease, aerobic exercise improved only some cognitive outcomes, whilst a mixed physical activity/exercise intervention improved executive function in 4 RCTs. Three SRs reported that mixed and home-based physical activity improved several cognitive (global and specific) and noncognitive (such as BPSD, quality of life, disability, and physical function tests) outcomes in people affected by dementia. These findings are substantially confirmed in people living in nursing home and affected by dementia (Table 4).

Risk of Bias Assessment in the SRs Included

Supplementary Figure 2A and B report the evaluation of the risk of bias, according to the ROBIS. Overall, the risk of bias affected more than half of the works included. The most important sources of possible risk of bias were the indication and the selection of the studies.

Discussion

In this umbrella review, including 27 articles and 28,205 participants with MCI or dementia, it was found that physical activity/exercise was able to improve cognitive and noncognitive outcomes in RCTs, but the strength of the evidence was overall very low-to-moderate and most SRs included had a high potential risk of bias.

It is estimated that the prevalence for MCI may range from 18.8% to 28.3% in people ≥ 60 years.[18] It is widely known that people affected by MCI are at greater risk of dementia than the general population, and the annual progression rates often range from 10% to 15%.[2,3] Among the risk factors that can increase the risk of transition from MCI to dementia, the role of sedentary behavior and physical activity is still poorly explored. For example, in a study including 810 people affected by MCI, it was found that sedentary behavior had no effect on the transition from MCI to dementia.[19] On the contrary, in our umbrella review, physical activity/exercise was able to significantly improve global cognition and specific cognitive tests. However, it should be noted that the evidence was limited by several biases encountered in the RCTs included (eg, small sample size) and some traditionally known limitations in RCTs including older people, such as a potential inclusion bias, confounding by education/social class/brain size/prior cognition.[20] Taken together, these findings suggest a potential role of physical activity/exercise in the prevention or delay in onset of dementia. However, reviews including observational studies exploring the potential role of physical activity/exercise in reducing the rate of the progression for MCI to dementia were not identified when carrying out the present umbrella review.

In people with dementia, physical activity/exercise was able to improve global cognition, but no specific areas of cognition. It may be hypothesized that the specific areas of cognition are difficult to explore in people with dementia, in particular in advanced stages.[21] Therefore, a floor effect for these tests is expected in more advanced forms of dementia.

We would like to briefly speculate regarding the possible explanations of our findings, in particular the benefits of physical activity/exercise on cognitive outcomes. First, it is widely known that physical activity/exercise significantly improves the management of cardiovascular risk factors (eg, diabetes, hypertension, dyslipidemia, and obesity) that are traditionally associated to poor cognitive performance.[22] Moreover, it is reported that physical activity/exercise may increase neurogenesis and synaptic plasticity.[11,23] Physical activity, especially aerobic exercise, is associated with increases in brain-derived neurotrophic factor (BDNF), a factor that can stimulate neuronal cell growth and maintain neurons in good status.[24] Third, using neuroimaging techniques, additional evidence for the impact of physical activity on brain function and structure is reported.[25–27] In this regard, physical activity/exercise might be a good predictor of long-term changes of brain structure, in particular brain volumes,[28] and risk for dementia, in particular for those who average more physical activity than their peers.[29]

In addition, physical activity/exercise interventions have an important role in improving several noncognitive outcomes including disability, falls, and neuropsychiatric symptoms in participants affected by dementia. All these outcomes are of clinical importance owing to a high level of co-occurrence and multimorbidity. For example, in one study, the incidence of falls in dementia was 9118 per 1000 person-years significantly higher than in controls.[30] The present umbrella review indicates that physical activity/exercise significantly decreased risk of falls by approximately 31% (equal to an absolute reduction in 204 falls every 1000 people affected by dementia) and also the number of falls (mean one fall over a mean of 6 months of follow-up). Therefore, we hypothesize that the beneficial effect of physical activity/exercise in decreasing the risk of falls and the number of falls may improve activities of daily living (ADL) since these 2 outcomes have been shown to be associated.[31] Finally, we found that physical activity/exercise may improve depression and BPSD, importantly this finding was also supported by the identified SRs without MA. Specifically, physical activity/exercise was able to significantly reduce 28% of the incidence of depressive symptoms in 15 different RCTs and, similarly, physical activity/exercise significantly reduced the severity of BPSD of 4.62 points on the NPI, which has a score range from 0 to 144. Briefly, we can speculate that physical activity/exercise may improve several aspects strictly related to BPSD, including the production of neurotransmitters, neurotrophins, BDNF, the reduction of oxidative stress and inflammatory levels, increase cerebral blood flow, regulate hypothalamic pituitary adrenal axis, and support of neurogenesis and synaptogenesis.[9] However, since this evidence is supported by a very low strength of the evidence, other studies are needed to make stronger these findings.

This study has limitations that must be taken into consideration when interpreting the findings. First, because the meta-analyses included studies with significant differences in design and population, clinical heterogeneity may have influenced the findings. For example, the present umbrella review does not attempt to identify characteristics of effective interventions and such analyses are beyond the scope of the present study. Future reviews on this topic that attempt to identify successful intervention components are now required. Physical activity/exercise adherence has been assessed using questionnaires, but there are limitations in such measures and

Table 4
Effect of Physical Exercise on Noncognitive Outcomes in MCI and Dementia

Certainty Assessment						No. of Patients		Effect		Certainty
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Physical Activity/ Exercise	Standard Care	Relative (95% CI)	Absolute (95% CI)	
Dementia, physical activity interventions home based, activities of daily living										
3	Not serious	Serious*	Not serious	Serious†	None	94	86	-	SMD **0.77** (0.17 to 1.37)	⨁⨁◯◯ LOW
Dementia, physical activity mixed interventions, depressive symptoms										
15	Not serious	Not serious	Not serious	Not serious	Publication bias strongly suspected‡	707	722	-	SMD −**0.18** (0.33 lower to 0.02 lower)	⨁⨁⨁◯ MODERATE
Dementia, physical activity mixed interventions, Behavioral and Psychological Symptoms in Dementia										
6	Very serious§	Very serious‖	Not serious	Not serious	None	497	564	-	MD −**4.62** (9.08 lower to 0.16 lower)	⨁◯◯◯ VERY LOW
Dementia, physical activity interventions home based, risk of falls in dementia										
2	Not serious	Not serious	Not serious	Serious†	Publication bias strongly suspected‡	90	90	**RR 0.69** (0.55 to 0.86)	-	⨁⨁◯◯ LOW
Dementia, physical activity interventions home based, number of falls in dementia										
3	Not serious	Not serious	Not serious	Serious†	None	134	137	-	MD -**1.06** (1.67 lower to 0.46 lower)	⨁⨁⨁◯ MODERATE
Dementia, physical activity mixed interventions, risk of falls										
3	Not serious	Not serious	Not serious	Serious†	None	189	182	**RR 0.69** (0.55 to 0.85)	**204 fewer per 1000** (from 296 fewer to 99 fewer)	⨁⨁⨁◯ MODERATE

*I^2 between 50% and 75%.
†Sample size less than 400 participants.
‡Egger's test (P value) <.05.
§One or more of the 3 criteria (randomization, masking, dropout rate >30%) is not met in >30% of trials included.
‖I^2 more than 75%.

objective monitors to record physical activity would provide more reliable estimates. Therefore, the future agenda should envision the use of objective monitors to record physical activity in patients with MCI or dementia, such as accelerometry. Moreover, the MAs included generically reported "dementia" that, on the contrary, can include different diagnoses and different severity. In this regard, the effect of physical activity/exercise in some less prevalent kinds of dementia (eg, Lewy bodies dementia or frontotemporal dementia) should be urgently explored by future RCTs. Furthermore, the literature on exercise training and cognition is characterized by poor quality research and trials, such as single center, small enthusiast led, and poor appreciation of the potential biases. Some recent trials have reported the importance of new technologies for improving physical exercise in people affected by MCI or dementia,[32] but larger RCTs are needed to confirm these findings. Finally, the evaluation of the quality of the included articles indicated that the risk of bias is relatively high for the vast majority.

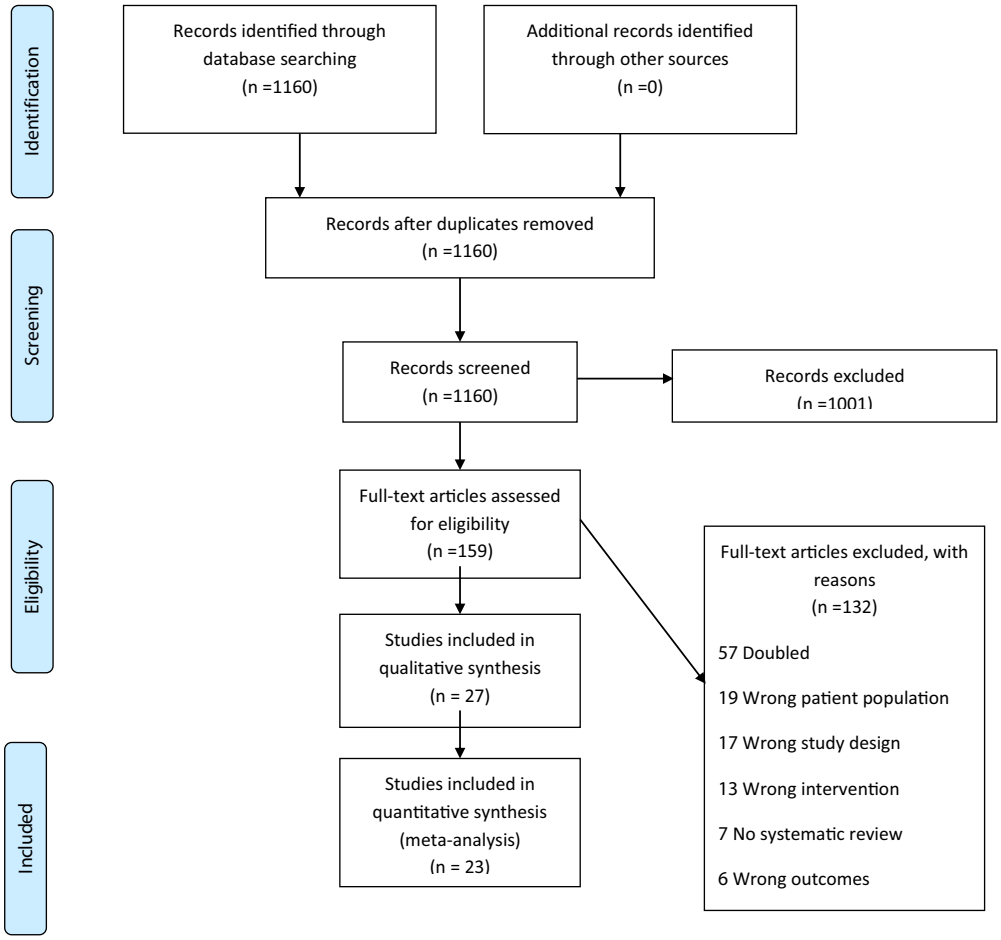
Conclusion

This umbrella review indicated that physical activity/exercise has a positive effect on several cognitive and noncognitive outcomes in people with MCI and dementia. However, these findings are supported by very low-to-moderate certainty of evidence indicating that other RCTs, particularly better structured in terms of physical activity/exercise programs and with larger sample sizes, are needed to fully support the use of physical activity/exercise in patients with MCI or dementia.

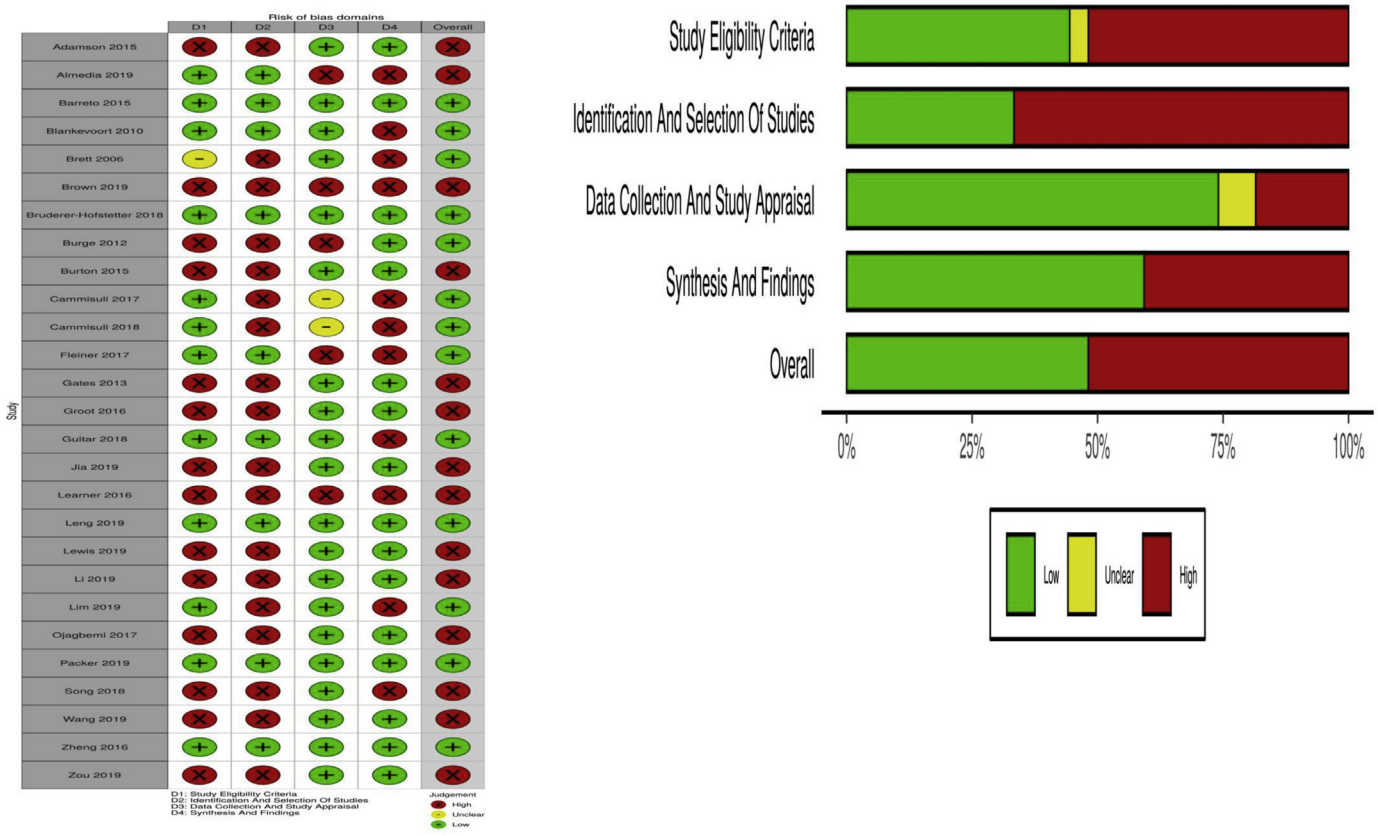
References

1. Prince M, Guerchet M, Prina M. The global impact of dementia 2013–2050. Alzheimer's Disease International; 2013. Available from: https://www.alz.co.uk/research/GlobalImpactDementia2013.pdf. Accessed September 17, 2020.
2. Xue H, Sun Q, Liu L, et al. Risk factors of transition from mild cognitive impairment to Alzheimer's disease and death: A cohort study. Compr Psychiatry 2017;78:91–97.
3. Farias ST, Mungas D, Reed BR, et al. Progression of mild cognitive impairment to dementia in clinic-vs community-based cohorts. Arch Neurol 2009;66:1151–1157.
4. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet 2017;390:2673–2734.
5. Liang J-h, Lu L, Li J-y, et al. Contributions of modifiable risk factors to dementia incidence: A Bayesian network analysis. J Am Med Dir Assoc; 2020.
6. Vancampfort D, Solmi M, Firth J, et al. The impact of pharmacologic and non-pharmacologic interventions to improve physical health outcomes in people with dementia: A meta-review of meta-analyses of randomized controlled trials. J Am Med Dir Assoc 2020;21:1410–1415.
7. 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.
8. Panza GA, Taylor BA, MacDonald HV, et al. Can exercise improve cognitive symptoms of Alzheimer's Disease? J Am Geriatr Soc 2018;66:487–495.
9. Veronese N, Solmi M, Basso C, et al. Role of physical activity in ameliorating neuropsychiatric symptoms in Alzheimer disease: A narrative review. Int J Geriatr Psychiatry 2019;34:1316–1325.
10. Lamb SE, Sheehan B, Atherton N, et al. Dementia and Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: Randomised controlled trial. BMJ 2018;361:k1675.
11. Nuzum H, Stickel A, Corona M, et al. Potential benefits of physical activity in MCI and dementia. Behavioural Neurology 2020;2020:7807856.
12. Folstein MF, Robins LN, Helzer JE. The mini-mental state examination. Arch General Psychiatry 1983;40:812.
13. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308.
14. Higgins JP, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions. Hoboken, NJ: John Wiley & Sons; 2019.
15. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol 2014;14:25.
16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–1558.
17. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924.
18. Ward A, Arrighi HM, Michels S, Cedarbaum JM. Mild cognitive impairment: Disparity of incidence and prevalence estimates. Alzheimers Dement 2012;8:14–21.
19. Lu Z, Harris TB, Shiroma EJ, et al. Patterns of physical activity and sedentary behavior for older adults with Alzheimer's disease, mild cognitive impairment, and cognitively normal in Hong Kong. J Alzheimer Dis 2018;66:1453–1462.
20. Shenkin SD, Harrison JK, Wilkinson T, et al. Systematic reviews: Guidance relevant for studies of older people. Age Ageing 2017;46:722–728.
21. Rascovsky K. A primer in neuropsychological assessment for dementia. Practical Neurology; 2016. Available from: https://practicalneurology.com/articles/2016-july-aug/a-primer-in-neuropsychological-assessment-for-dementia. Accessed September 17, 2020.
22. de La Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. Cardiovasc Psychiatry Neurol 2012;2012:367516.
23. Boecker H. On the emerging role of neuroimaging in determining functional and structural brain integrity induced by physical exercise: Impact for predictive, preventive, and personalized medicine. EPMA J 2011;2:277–285.
24. Currie J, Ramsbottom R, Ludlow H, et al. Cardio-respiratory fitness, habitual physical activity and serum Brain Derived Neurotrophic Factor (BDNF) in men and women. Neurosci Lett 2009;451:152–155.
25. Chen L-Z, Yuan X, Zhang Y, et al. Brain functional specialization is enhanced among Tai Chi Chuan practitioners. Arch Phys Med Rehabil 2020;101:1176–1182.
26. Lautenschlager NT, Cox K, Cyarto EV. The influence of exercise on brain aging and dementia. Biochim Biophys Acta 2012;1822:474–481.
27. Yue C, Zou L, Mei J, et al. Tai Chi training evokes significant changes in brain white matter network in older women. Healthcare 2020;8:57.
28. Valenzuela PL, Castillo-García A, Morales JS, et al. Exercise benefits on Alzheimer's disease: State-of-the-science. Ageing Res Rev 2020;62:101108.
29. Erickson KI, Raji CA, Lopez OL, et al. Physical activity predicts gray matter volume in late adulthood: The Cardiovascular Health Study. Neurology 2010;75:1415–1422.
30. Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and prediction of falls in dementia: A prospective study in older people. PLoS One 2009;4:e5521.
31. Gill TM, Murphy TE, Gahbauer EA, Allore HG. Association of injurious falls with disability outcomes and nursing home admissions in community-living older persons. Am J Epidemiol 2013;178:418–425.
32. Taylor ME, Close JC, Lord SR, et al. Pilot feasibility study of a home-based fall prevention exercise program (StandingTall) delivered through a tablet computer (iPad) in older people with dementia. Australas J Ageing; 2019.

Appendix



Supplementary Fig. 1. PRISMA flow chart.



Supplementary Fig. 2. (A, B) ROBIS quality assessment of the included meta-analyses.

Supplementary Table 1
Search Strategy for Medline, Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to December 31, 2019 Search Date: 2019–12–31

#	Searches	Results
1	dementia/	49095
2	alzheimer disease/	90423
3	exp dementia, vascular/	6477
4	exp frontotemporal lobar degeneration/	4048
5	lewy body disease/	3083
6	Cognitive Dysfunction/	14399
7	alzheimer*.kf,tw.	141531
8	dementia.kf,tw.	105140
9	mild cognitive impairment.kf,tw.	15851
10	cognitive decline.kf,tw.	20760
11	exp Exercise/	186267
12	exp Physical Therapy Modalities/	147834
13	Occupational Therapy/	12904
14	exercise.kf,tw.	255703
15	exergam*.kf,tw.	604
16	physical* activ*.kf,tw.	111213
17	physiotherapy.kf,tw.	18695
18	physical therapy.kf,tw.	20070
19	occupational therapy.kf,tw.	10749
20	training.kf,tw.	389690
21	"systematic review"/	117716
22	meta-analysis/	108185
23	(systematic adj1 review).kf,tw.	144289
24	meta-analys*.kf,tw.	158520
25	or/1–10	243864
26	or/11–20	870308
27	or/21–24	267732
28	25 and 26	9695
29	25 and 26 and 27	1160

Supplementary Table 2
Criteria Evidence for the GRADE

Downgrade	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias
−1	If 1 or more of the 3 criteria (randomization, masking, dropout rate ≤30%) is not met in 10–30% of trials included in the systematic review	I^2 50–74%	The question being addressed by the guideline panel is different from the available evidence regarding the PICO or regarding the characteristics of those who will deliver the intervention	(a) The overall number of individuals included in trials is low (less than 400 individuals, both treatment arms) OR (b) the 95% confidence interval includes both 1) no effect and 2) appreciable benefit (RR: ≤0.75) or appreciable harm (RR: ≥1.25)*	-
−2	If 1 or more of the 3 criteria (randomization, masking, dropout rate ≥30%) is not met in >30% of trials included in the systematic review	$I^2 \geq 75\%$	The question being addressed by the guideline panel is markedly different from the available evidence regarding the PICO or regarding the characteristics of those who will deliver the intervention	(a) the overall number of individuals included in trials is very low (fewer than 400 individuals, both treatment arms) AND (b) the 95% confidence interval includes both 1) no effect and 2) appreciable benefit (RR: ≤0.75) or appreciable harm (RR: ≥1.25)*	Egger's test (P value) <.05

PICO, Population, Intervention, Comparison, and Outcomes.
For dichotomous outcomes, "*no effect*" means an estimate with a confidence interval that *crosses 1*; appreciable benefit or appreciable harm means that the upper or lower confidence limit crosses a risk of 1.25 or 0.75.
*For continuous outcomes, "*no effect*" means an SMD with a confidence interval that *crosses zero*; appreciable benefit or appreciable harm means that the upper or lower confidence limit crosses an effect size of 0.5 in either direction.

Supplementary Table 3
List of the References Included in the Umbrella Review

Blankevoort CG, van Heuvelen MJ, Boersma F, et al. Review of effects of physical activity on strength, balance, mobility and ADL performance in elderly subjects with dementia. Dement Geriatr Cogn Disord 2010;30:392–402.

Burge E, Kuhne N, Berchtold A, et al. Impact of physical activity on activity of daily living in moderate to severe dementia: a critical review. Eur Rev Aging Phys Act 2012;9:27–39.

Gates N, Fiatarone Singh MA, et al. 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.

Adamson BC, Ensari I, Motl RW. Effect of exercise on depressive symptoms in adults with neurologic disorders: A systematic review and meta-analysis. Arch Phys Med Rehabil 2015;96:1329–1338.

Barreto Pde S, Demougeot L, Pillard F, et al. Exercise training for managing behavioral and psychological symptoms in people with dementia: A systematic review and meta-analysis. Ageing Res Rev 2015;24(Pt B):274–285.

Burton E, Cavalheri V, Adams R, 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;10:421–434.

Groot C, Hooghiemstra AM, Raijmakers PG, et al. The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. Ageing Res Rev 2016;25:13–23.

Zheng G, Xia R, Zhou W, et al. 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.

Cammisuli DM, Innocenti A, Franzoni F, Pruneti C. Aerobic exercise effects upon cognition in Mild Cognitive Impairment: A systematic review of randomized controlled trials. Archives italiennes de biologie 2017;155:54–62.

Fleiner T, Leucht S, Forstl H, et al. Effects of short-term exercise interventions on behavioral and psychological symptoms in patients with dementia: A systematic review. J Alzheimers Dis 2017;55:1583–1594.

Lewis M, Peiris CL, Shields N. Long-term home and community-based exercise programs improve function in community-dwelling older people with cognitive impairment: a systematic review. J Physiother 2017;63:23–29.

Bruderer-Hofstetter M, Rausch-Osthoff AK, Meichtry A, et al. Effective multicomponent interventions in comparison to active control and no interventions on physical capacity, cognitive function and instrumental activities of daily living in elderly people with and without mild impaired cognition - A systematic review and network meta-analysis. Ageing Res Rev 2018;45:1–14.

Cammisuli DM, Innocenti A, Fusi J, et al. Aerobic exercise effects upon cognition in Alzheimer's Disease: A systematic review of randomized controlled trials. Archives italiennes de biologie 2018;156:54–63.

Guitar NA, Connelly DM, Nagamatsu LS, et al. The effects of physical exercise on executive function in community-dwelling older adults living with Alzheimer's-type dementia: A systematic review. Ageing Res Rev 2018;47:159–167.

Leng M, Liang B, Zhou H, et al. Effects of physical exercise on depressive symptoms in patients with cognitive impairment: A systematic review and meta-analysis. J Nerv Ment Dis 2018;206:809–823.

Song D, Yu DSF, Li PWC, Lei Y. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis. Int J Nurs Stud 2018;79:155–164.

Almeida SIL, Gomes da Silva M, Marques A. Home-based physical activity programs for people with dementia: Systematic review and meta-analysis [published online ahead of print December 20, 2019]. Gerontologist.

Brown SR, Yoward S. The effectiveness of home-based exercise programmes on mobility and functional independence in community-dwelling adults with Alzheimer's disease: a critical review. Int J Ther Rehabil 2019;26:1–14.

Jia RX, Liang JH, Xu Y, Wang YQ. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: A meta-analysis. BMC Geriatr 2019;19:181.

Li X, Guo R, Wei Z, et al. Effectiveness of exercise programs on patients with dementia: A systematic review and meta-analysis of randomized controlled trials. Biomed Res Int 2019;2019:2308475.

Lim KH, Pysklywec A, Plante M, Demers L. The effectiveness of Tai Chi for short-term cognitive function improvement in the early stages of dementia in the elderly: a systematic literature review. Clin Interv Aging 2019;14:827–839.

Ojagbemi A, Akin-Ojagbemi N. Exercise and quality of life in dementia: A systematic review and meta-analysis of randomized controlled trials. J Appl Gerontol 2019;38:27–48.

Packer R, Ben Shlomo Y, Whiting P. Can non-pharmacological interventions reduce hospital admissions in people with dementia? A systematic review. PLoS One 2019;14:e0223717.

Wang S, Yin H, Wang X, et al. Efficacy of different types of exercises on global cognition in adults with mild cognitive impairment: A network meta-analysis. Aging Clin Exp Res 2019;31:1391–1400.

Zou L, Loprinzi PD, Yeung AS, et al. The beneficial effects of mind-body exercises for people with mild cognitive impairment: a systematic review with meta-analysis. Arch Phys Med Rehabil 2019;100:1556–1573.

Learner NA, Williams JM. Can physical activity be used to maintain cognitive function in nursing home residents with dementia? A literature review. Phys Ther Rev 2016;21:184–191.

Brett L, Traynor V, Stapley P. Effects of physical exercise on health and well-being of individuals living with a dementia in nursing homes: A systematic review. J Am Med Dir Assoc 2016;17:104–116.

Supplementary Table 4
Effect of Physical Exercise on Cognitive Outcomes in MCI and Dementia

Certainty Assessment							No. of Patients		Effect		Certainty
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Physical Activity/ Exercise	Standard Care	Relative (95% CI)	Absolute (95% CI)	
Global cognition (in AD) (mixed physical activity intervention)											
13	Randomized trials	Very serious*	Very serious†	Not serious	Not serious	Publication bias strongly suspected‡	342	331	-	SMD **1.10** (0.65 to 1.64)	⊕◯◯◯ VERY LOW
Global cognition (in dementia) (mixed physical activity intervention)											
19	Randomized trials	Not serious	Very serious†	Not serious	Not serious	None	433	405	-	SMD **0.48** (0.22 to 0.74)	⊕⊕◯◯ LOW
Short-term memory (in MCI) (mind-body intervention)											
12	Randomized trials	Very serious*	Not serious	Not serious	Not serious	None	354	389	-	SMD **0.74** (0.57 to 0.91)	⊕⊕◯◯ LOW
Short-term memory (in MCI) (Tai Chi intervention)											
4	Randomized trials	Very serious*	Not serious	Not serious	serious§	None	114	240	-	SMD **0.77** (0.45 to 1.09)	⊕◯◯◯ VERY LOW
Global cognition (in MCI) (mind-body intervention)											
9	Randomized trials	Very serious*	Not serious	Not serious	Not serious	None	425	557	-	SMD **0.36** (0.2 to 0.52)	⊕⊕◯◯ LOW
Executive function (in MCI) (mind-body intervention)											
9	Randomized trials	Very serious*	Not serious	Not serious	Not serious	None	424	476	-	SMD **0.42** (0.63 lower to 0.21 lower)	⊕⊕◯◯ LOW
Global cognition (in MCI) (mixed physical activity intervention)											
8	Randomized trials	serious‖	Not serious	Not serious	Not serious	None	342	334	-	SMD **0.30** (0.11 to 0.49)	⊕⊕⊕◯ MODERATE
Global cognition (in MCI) (resistance training intervention)											
4	Randomized trials	Very serious*	Serious**	Not serious	Serious§	None	77	69	-	SMD **0.80** (0.29 to 1.31)	⊕◯◯◯ VERY LOW
Visuospatial executive function (in MCI) (mind-body intervention)											
4	Randomized trials	Very serious*	Not serious	Not serious	Not serious	None	163	162	-	SMD **0.36** (0.07 to 0.64)	⊕⊕◯◯ LOW
Delayed memory (in MCI) (aerobic exercise intervention)											
7	Randomized trials	Not serious	Serious**	Not serious	Not serious	None	638	675	-	SMD **0.26** (0.06 to 0.46)	⊕⊕⊕◯ MODERATE

(*continued on next page*)

Supplementary Table 4 (*continued*)

Certainty Assessment							No. of Patients		Effect		Certainty
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Physical Activity/ Exercise	Standard Care	Relative (95% CI)	Absolute (95% CI)	
Attention (in MCI) (mind-body intervention)											
5	Randomized trials	Very serious*	Not serious	Not serious	Not serious	None	183	182	-	SMD **0.39** (0.07 to 0.72)	⊕⊕◯◯ LOW

*One or more of the 3 criteria (randomization, masking, dropout rate >30%) is not met in >30% of trials included.
†$I^2 \geq 75\%$.
‡Egger's test (*P* value) <.0001
§Total sample size <400 participants.
‖One or more of the 3 criteria (randomization, masking, dropout rate <30%) is not met in 10% to 30% of trials included.
**I^2 between 50% and 75%.