# PHYSICAL ACTIVITY AND EXERCISE IN MILD COGNITIVE IMPAIRMENT AND DEMENTIA: AN UMBRELLA REVIEW OF INTERVENTION AND OBSERVATIONAL STUDIES

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# ABSTRACT

**Objectives:** The aim of this umbrella review was to determine the effect of physical activity/exercise on improving cognitive and non-cognitive 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 includedparticipants not following any pre-specified physical activity/exercise intervention or following the same standard protocol with the intervention group.

**Methods:** The protocol was registered in PROSPERO (CDR 164197).Major databases were searched until 31 December 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 1,160 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’s 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 non-cognitive 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 non-cognitive outcomes in people with MCI and dementia, but RCTs, with low risk of bias/confounding, are still needed to confirm these relationships.

# INTRODUCTION

The number of people living with dementia worldwide in 2015 was estimated at 47.5 million, reaching 75.6 million in 2030.[1](#_ENREF_1) Future projections are indicating that this number will be 135.46 million in 2050.[1](#_ENREF_1) Approximately 7.7 million new cases of dementia are anticipated each year.[1](#_ENREF_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 often range from 10% to 15%.[2](#_ENREF_2),[3](#_ENREF_3)

Unfortunately, there are no curative treatments for dementia and so epidemiological research regarding risk factors for this disease is of importance. In recent research, it has been estimated that 3% of dementia cases could be prevented by increasing levels of free-living physical activity[4](#_ENREF_4),[5](#_ENREF_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](#_ENREF_6)

In this regard, older people who are physically active are more likely to maintain cognition than those who are not.[4](#_ENREF_4) In a meta-analysis including fifteen 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](#_ENREF_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](#_ENREF_8) Moreover, physical activity in general and exercise interventions in particular might help in ameliorating Behavioral and Psychological Symptoms in Dementia (BPSD).[9](#_ENREF_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](#_ENREF_10)

The effect of physical activity/exercise in mild cognitive impairment (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 non-cognitive outcomes in this special population at higher risk for dementia.[11](#_ENREF_11)

Given this background, the aim of this umbrella review, promoted by the European Geriatric Medicine Society (EuGMS), is to understand the effect of physical activity/exercise on improving cognitive and non-cognitive 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 31st December 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:

a) systematic reviews [SRs] with or without meta-analyses [MAs] of interventions of only RCTs regarding physical activity/exercise interventions in people with MCI;

b) 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;

c) SRs with or without MAs of interventions of only randomized controlled trials (RCTs) regarding physical activity/exercise interventions in people affected by dementia;

We included any form of physical activity (i.e. any movement that is carried out by the skeletal muscles that requires energy), as defined by authors. For exercise (i.e. 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 (e.g. aerobic and resistance exercise together), physiotherapy, and physical activity during occupational therapy. As controls, we includedparticipants not following any pre-specified physical activity/exercise intervention or following the same standard protocol with the intervention group additionally receiving an exercise/physical activity component.

When more than one 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](#_ENREF_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) Behavioral and Psychological Symptoms in Dementia (BPSD), measured with validated tests such as the neuropsychiatric inventory (NPI)[13](#_ENREF_13);

3) adverse events (e.g. mortality, falls, fractures, hospitalizations, nursing home admissions);

4) medical events (e.g. stroke);

5) health-related quality of life;

6) functional performance tests (e.g. gait speed, chair rise, balance, Short Physical Performance Battery (SPPB), aerobic capacity, strength).

## Data extraction

Data extraction was led by two independent reviewers (JD, GG) and disagreements were resolved through consensus with the senior author (NV). This task proceeded with a two-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 (for example, 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](#_ENREF_14) The MD is a standard statistic that measures the absolute difference between the mean value between two groups in a clinical trial and it is commonly used as an effect size when outcome measurements in all studies are made on the same scale. [14](#_ENREF_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 four 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](#_ENREF_15) Between-study inconsistency was estimated with the *I2* metric, with values >50% indicative of high heterogeneity.[16](#_ENREF_16)All statistical analyses were conducted in Stata, version 14.0 (StataCorp).

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](#_ENREF_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 by four 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](#_ENREF_17)

# RESULTS

## Literature search

As shown in **Supplementary** **Figure 1**, 1,160 articles were initially included. Of them, 159 full-texts were retrieved, with 27 articles finally included (18 MAs and 9 SRs without MA) (references 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.

## 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’s 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 non-cognitive 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 equal to ; 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 two 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 four RCTs. Three SRs reported that mixed and home-based physical activity improved several cognitive (global and specific) and non-cognitive (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 systematic reviews included

**Supplementary Figures 2a and 2b** 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 non-cognitive outcomes in RCTs, but the strength of the evidence was overall very low-to-moderate and the majority of SRs included had a high potential risk of bias.

It is estimated that the annual prevalence for MCI may range from 18.8% to 28.3% in people > 60 years.[18](#_ENREF_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](#_ENREF_2),[3](#_ENREF_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](#_ENREF_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 (e.g. 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](#_ENREF_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](#_ENREF_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 (e.g., diabetes, hypertension, dyslipidemia, and obesity) that are traditionally associated to poor cognitive performance.[22](#_ENREF_22) Moreover, it is reported that physical activity/exercise may increase neurogenesis and synaptic plasticity.[11](#_ENREF_11),[23](#_ENREF_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](#_ENREF_24) Third, using neuroimaging techniques, additional evidence for the impact of physical activity on brain function and structure is reported.[25](#_ENREF_25),[26](#_ENREF_26)[27](#_ENREF_27) In this regard, physical activity/exercise might be a good predictor of long-term changes of brain structure, in particular brain volumes[28](#_ENREF_28), and risk for dementia, in particular for those who average more physical activity than their peers.[29](#_ENREF_29)

In addition, physical activity/exercise interventions have an important role in improving several non-cognitive 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 9,118 per 1,000 person-years significantly higher than in controls.[30](#_ENREF_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 1,000 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 two outcomes have been shown to be associated.[31](#_ENREF_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 Neuropsychiatry Inventory, 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.[32](#_ENREF_32) 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, since the meta-analyses included studies with significant differences in design, 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 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 MCI/dementia patients, 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 (e.g. 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[33](#_ENREF_33), 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 non-cognitive 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 for fully supporting the use of physical activity/exercise in our patients.

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