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Effectiveness of exercise and physical activity interventions to improve long-term patient-relevant cognitive and non-cognitive outcomes in people living with mild cognitive impairment: a protocol of a systematic review and meta-analysis

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ABSTRACT

Introduction Mild cognitive impairment (MCI) is a clinical syndrome characterised by persistent cognitive deficits that do not yet fulfil the criteria of dementia. Delaying the onset of dementia using secondary preventive measures such as physical activity and exercise can be a safe way of reducing the risk of further cognitive decline and maintaining independence and improving quality of life. The aim is to systematically review the literature to assess the effectiveness of physical activity and exercise interventions to improve long-term patient-relevant cognitive and non-cognitive outcomes in people living with MCI, including meta-analyses if applicable.

Methods and analysis We will systematically search five electronic databases from 1995 onward to identify trials reporting on the effectiveness of physical activity and exercise interventions to improve long-term (12+ months) patient-relevant cognitive and non-cognitive outcomes in adults (50+ years) with MCI. Screening procedures, selection of eligible full-texts, data extraction and risk of bias assessment will be performed in dual-review mode. Additionally, the reporting quality of the exercise interventions will be assessed using the Consensus on Exercise Reporting Template. A quantitative synthesis will only be conducted if studies are homogeneous enough for effect sizes to be pooled. Where quantitative analysis is not applicable, data will be represented in a tabular form and synthesised narratively. People living with MCI will be involved in defining outcome measures most relevant to them in order to assess in how far randomised controlled trials report endpoints that matter to those concerned.

Ethics and dissemination Results will be disseminated to both scientific and lay audiences by creating a patient-friendly video abstract. This work will inform professionals in primary care about the effectiveness of physical activity and exercise interventions and support them to make evidence-based exercise recommendations for the secondary prevention of dementia in people living with MCI. No ethical approval required.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ People living with mild cognitive impairment will be involved in a workshop to discuss preferences regarding patient relevant outcomes of scientific physical activity and exercise trials designed to maintain cognitive health and independence as well as delay or prevent the onset of dementia.

⇒ Reporting quality of physical activity and exercise intervention details will be assessed allowing for an estimation of potential research waste that may impede translation of research findings into recommendations for physical activity and exercise in general practice.

⇒ Results of this work will be disseminated to both scientific and lay audiences by means of a patient-friendly video abstract. The dissemination strategy involves patient organisations.

⇒ We expect some heterogeneity with regard to outcome parameters, which may limit opportunity of quantitative synthesis.

INTRODUCTION

Mild cognitive impairment (MCI) is a clinical syndrome characterised by persistent cognitive deficits that do not yet fulfil the criteria of dementia.[1] According to the fifth version of the diagnostic and statistical manual of mental disorders (DSM-5), mild neurocognitive disorders can affect several cognitive domains such as complex attention, executive

function, learning and memory, language, perceptual motor abilities as well as social cognition.[2] These symptoms of MCI are similar to those of dementia but less severe and do not yet interfere significantly with activities of daily living and independence.

Prevalence of MCI increases with age, affecting 6.7% of those aged 60–64 years and up to 25.2% of those aged 80–84 years.[1] Compared with cognitively healthy subjects, longitudinal evidence on mortality suggests an elevated risk of death in individuals with MCI.[3] People living with MCI have an elevated risk of developing dementia over time. The Cognitive Decline Group of EIPAHA reports a yearly conversion rate of 15%–41%.[4] In the absence of a curative therapy, people living with MCI progressing to dementia face the burden of increasing dysfunctions in memory, language and visuospatial abilities. They also may develop other typical symptoms of dementia, including behavioural and personality changes, physical dysfunction, agitation, apathy, difficulties controlling emotions, social withdrawal, loss of empathy,[5] as well as impaired daily life activities[6] and quality of life.[7] Additionally, deterioration in the quality of life may also affect caregivers and family members.[8] In 2015, the global cost of dementia was estimated to total US$818 billion.[9] Accordingly, costs of care may be substantially reduced by delaying the onset of dementia in people living with MCI using secondary preventive measures.[10]

WHO guidelines on risk reduction of cognitive decline and dementia separately focus on secondary prevention and summarise key interventions aimed at slowing down cognitive decline and delaying the onset of dementia.[11] Among other measures, the WHO report concludes that physical activity may be recommended to people living with MCI to reduce the risk of further cognitive decline highlighting that recommendations rely on rather low-quality evidence.[12] American and Australian exercise guidelines for people living with MCI have come to similar conclusions.[1 13]

Therefore, while the positive effects of physical activity and exercise on dementia prevention in healthy older populations are well documented, such evidence is relatively scarce for people living with MCI, especially regarding important long-term effects. Many systematic reviews and meta-analyses have been published that synthesise interventional evidence on cognitive and non-cognitive effects of physical activity and exercise in patients with MCI and recently published umbrella reviews highlight the quantity of evidence in this field.[14 15] However, we are not aware of an evidence synthesis strictly including long-term interventions as well as long-term outcomes of physical activity and exercise in MCI patients and, therefore, intend to address this research gap. There is a need to understand whether physical activity and exercise is effective in improving health of people living with MCI in the long run. This is all the more important given that, in real life, maintaining exercise regimens and physical activities in the patients' daily lives can be a challenge.

Moreover, evidence is lacking on how best to deliver physical activity and exercise interventions, specifically for people living with MCI. The problem of unsatisfactory reporting in non-pharmacological trials, including exercise research, makes it impossible to replicate and implement poorly described yet effective therapies in practice.[16–18] The recently updated practice guidelines of the American Academy of Neurology advise clinicians to 'recommend physical exercise' (level B recommendation).[1] However, the nebulous recommendation of exercise per se may be unsatisfactory for clinicians and patients alike, as it is unclear exactly what kind of physical activity and exercise should be carried out or prescribed.[19]

The aim of this project is to systematically review the literature to assess the effectiveness of physical activity and exercise interventions to improve long-term patient-relevant cognitive and non-cognitive outcomes in people living with MCI, including meta-analyses if applicable. Secondary research questions are how well the included trials report intervention details in order to allow health professionals to prescribe physical activity and exercise for people living with MCI in clinical practice and in how far the endpoints reported in included randomised controlled trials (RCTs) are in line with patient preferences.

METHODS AND ANALYSIS

The present protocol will follow the Preferred Reporting System Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist (see online supplemental additional file 1).[20] The protocol has been registered with PROSPERO and will be updated with new versions in case of any future changes to the protocol.

Design

This is a full systematic review that will include meta-analyses if applicable.

Criteria for considering studies for this review

Type of studies

We will include full-text RCTs (pilot, parallel-arms(s), cluster and cross-over) that allow the separate analysis of an exercise or physical activity intervention versus any placebo-designed or active (but physically non-active) control group (CG) in an MCI population.

Studies will be restricted to a minimum intervention length of 24 weeks and must report (non-)cognitive outcomes at least 48 weeks after the exercise intervention began. Studies outside previously described designs will be excluded. Study designs with mixed population that do not report separate results of the MCI subgroup will not be eligible.

Type of participants

We will select studies involving adult individuals (50+ years) diagnosed with MCI (all cause). A diagnosis of MCI can be based on commonly applied criteria, such as

Winblad or Petersen criteria,[21 22] or on the study authors' individual definition of MCI as long as it involves a sound diagnosis by a neuropsychiatrist. Accordingly, studies including participants based on subjective cognitive complaint or objective cognitive impairment alone, or including asymptomatic participants at increased risk of dementia will not be included. Healthy population, population with a diagnosis of dementia or cognitive impairment caused by traumatic injury or psychiatric disorders such as major depression will be excluded. Studies including participants with MCI experiencing other comorbidities or multimorbidity will be eligible.

Regarding higher incidence rates in low-income and middle-income countries,[23] and to ensure some external validity, the reviewed populations will not be confined to specific geographical regions, cultures or ethnicities.

Type of intervention

Studies will be screened for interventions in which physical activity or exercise is the only intervention, so that it is possible to isolate and measure its effect. For this review, physical activity is broadly defined as any form of structured exercise, recreational activity or bodily movement that results in elevated energy expenditure.[12] Hence, interventions will not be restricted to specific types of physical activity or exercise (ie, aerobic exercise, psychomotor activity, strength training and multicomponent exercise), individualised intensity thresholds, volumes, frequencies, session durations, delivery modes or settings. Meditation, mindfulness programmes and social support therapies, and those whose primary focus is not physical activity will not be considered eligible. As it is unlikely that hard endpoints such as the incidence of dementia will change over very short intervention periods, intervention durations shorter than 24 weeks will be considered ineligible.

Type of comparator

We will include studies with any well-designed placebo treatment to avoid high risk of bias resulting from no-treatment CGs. More specifically, acceptable comparison groups will be those undertaking sham exercise (ie, stretching, toning, face or finger exercise) and, to control for the effects of social interaction, those participating in active (but physically non-active) CGs such as social visits and educational sessions. To ensure some homogeneity, head-to-head comparisons of various exercise stimuli, multimodal interventions such as combined exercise and cognitive training, and other solitary therapeutic activities, will be excluded.

Outcomes

According to the German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), patient-relevant endpoints are defined as both the intended and unintended effects of an intervention to evaluate the following parameters: mortality, morbidity (including adverse events) and health-related quality of life.[24] Since mortality is unlikely to be assessable due to the design aspects inherent in RCTs (small sample sizes and short follow-up periods), we will include any outcome and follow-up measure from the list below that was assessed a minimum of 48 weeks after beginning an exercise or physical activity intervention:

- Incidence of dementia
- Incidence of neuropsychiatric symptoms (ie, the Neuropsychiatric Inventory[25])
- Global cognition and domain-specific cognition (ie, Mini-Mental State Exam (MMSE)[26] and Alzheimer's Disease Assessment Scale-cognitive[23])
- Domain-specific cognition (ie, Trail Making Test[27])
- (Instrumental) activities of daily living (ie, Disability Assessment for Dementia[28]).
- (Health-related) quality of life (ie, Dementia Quality of Life Instrument[29])
- Healthcare utilisation (ie, nursing home admissions)
- Caregiver outcomes
- Psychosocial functioning such as mood, stress, depressive symptoms and social interaction (ie, Beck's Depression Inventory[30] and Philadelphia Geriatric Center Moral Scale[31]).
- Physical functioning (ie, aerobic fitness, strengths and balance)
- Pain
- Motivational parameters (ie, self-efficacy, locus of control and perceived barriers/enablers to maintain and initiate exercise).
- Incidence of adverse events.
- Neurobiological outcomes/biomarkers (ie, brain volume)
- Compliance parameters (ie, attendance rate, drop-out rate and adherence).

However, depending on the results of a workshop with people living with MCI conducted prior to extracting results, focus might be put on those outcome measures which have been identified as to be most relevant to them. Table 1 provides an overview on the exclusion and inclusion criteria.

Search methods used to identify studies

Electronic searches

We will search the following electronic sources from 1995 using a combination of Medical Subject Headings and keywords: MEDLINE, Embase, PsycINFO, SPORTDiscus and Cochrane's Central Register of Controlled Trials. The 1995 starting date was chosen because the first use of the term MCI as an independent diagnostic category occurred in that year.[32] A combination of subject headings and free-text terms will be used for the following key search areas such as participants, intervention and study types. The electronic search strategy for all databases is provided in online supplemental additional file 2.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Type of studies	
► Full-length RCTs: pilot, parallel-arms(s), cluster and cross-over ► No restriction in study setting. Language of the studies limited to German, Spanish and English. Publication date limited to 1995 onward	► Studies outside previously described designs ► Study protocols
Types of participants	
► Adult individuals: 50+ years (mean/median age, at least 80% of results stratified for this age group) ► MCI (all cause) based on commonly applied criteria or on the study authors' individual definition of MCI as long as it involves a sound diagnosis by a neuropsychiatrist ► Patients with MCI with comorbidities or multimorbidity were eligible	► Healthy participants ► Dementia or cognitive impairment caused by traumatic injury or psychiatric disorders such as major depression ► Study does not report how the diagnosis of MCI was achieved ► MCI diagnosis based on subjective cognitive complaint alone ► MCI diagnosis based on objective cognitive impairment alone ► Studies including mixed populations of MCI/healthy/dementia populations where results are not separately reported for patients with MCI ► Participants at increased risk of dementia but asymptomatic
Intervention	
► Exercise or physical activity must be the only intervention and must last 24+ weeks, independent of type, intensity, volume, frequency, session duration, delivery mode and setting	► Meditation, mindfulness-programmes, social support therapies and those whose primary focus is not physical activity (defined as any form of structured exercise, recreational activity or bodily movement that results in elevated energy expenditure)
Comparator	
► Any well-designed placebo treatments such as sham exercise (ie, stretching, toning, face or finger exercise). ► Active (but physically non-active) CGs (ie, social visits and educational sessions)	► Head-to-head comparisons of various exercise stimuli ► Multimodal interventions such as combined exercise or physical activity and cognitive training, and other solitary therapeutic activities
Outcomes	
Cognitive and non-cognitive outcomes at least 48 weeks after the exercise intervention began: ► Incidence of dementia ► Incidence of neuropsychiatric symptoms ► Global cognition and domain-specific cognition ► Domain-specific cognition ► (Instrumental) activities of daily living ► (Health-related) quality of life ► Healthcare utilisation ► Caregiver outcomes ► Psychosocial functioning ► Physical functioning ► Motivational parameters ► Incidence of adverse events ► Neurobiological outcomes ► Compliance parameters	► Studies outside previously described outcomes

CGs, control groups; MCI, mild cognitive impairment; RCTs, randomised controlled trials.

Other resources

Additionally, we will hand search the Cochrane Dementia and Cognitive Improvement Group Specialised Register ALOIS for all results in the diagnosis category 'MCI' and the intervention categories of 'exercise or physical activity'. Finally, a search of the Cochrane Database of Systematic Reviews will be performed to retrieve primary studies from the screening references of relevant systematic reviews. Articles will be confined to published English, Spanish and German language RCTs. If clinical trial registration entries without a corresponding full-text publication will be identified as potentially eligible for inclusion, authors will be contacted.

Study records

Data management

Bibliographic details of all identified references will be downloaded as RIS files and then uploaded into COVIDENCE software[33] for title, abstract and full-text screening. Duplicates will be removed.

Selection of studies

Two review authors (MD and AIG-G) will independently screen the title and abstract of every identified study to determine which should be assessed further. Before screening, a stepwise calibration test will be performed on a sample of 30 studies,[34] with the aim of achieving 80% agreement between reviewers. If 80% agreement is not reached, our inclusion and exclusion criteria will be refined, and the calibration will be repeated until this threshold is met. We will report star to the inclusion and exclusion criteria that result from the calibration test as deviations from the published protocol. The full text of potentially eligible papers will then be retrieved and independently assessed for eligibility by two reviewers (MD and AIG-G). Any discrepancy will be resolved through discussion and consensus, and if needed with the help of a third reviewer (ASiebenhofer). We will present a PRISMA flow-chart to illustrate the study-selection process.[20]

Data collection

Two review authors (MD and AIG-G) will independently extract key study and participant characteristics from all studies that fulfil the inclusion criteria, and report data on outcomes. Any disagreement will be resolved by discussion, or, if necessary, by a third author (ASiebenhofer). A calibration test like the one described above will precede data extraction.

Data items

The following data will be independently extracted by two researchers (MD and AIG-G):

- Author, country, study type, setting and recruitment, sample size, inclusion and exclusion criteria, intervention design (programme duration, session duration, frequency, intensity, delivery mode and exercise mode), control condition, all cognitive and non-cognitive outcome measures, length and number of follow-ups.
- Patient demographics (mean age, gender, mean MMSE scores, baseline fitness level and education).
- Main results, conclusive quote, quality of evidence, degree of compliance with the Consensus on Exercise Reporting Template (CERT), source of funding.

A data extraction framework is provided in online supplemental additional file 3.

Dealing with duplicate and associated publications

In the event of multiple publications of a single study, we will maximise the information yield by collating all available data and using the most complete data set, aggregated across all known publications.

Assessment of risk of bias in included studies

Two authors (MD and AIG-G) will independently assess risk of bias of the included RCTs using the Cochrane Collaboration's Risk of Bias tool (V.1.0)[35] in accordance with the application guidance of the Cochrane Handbook for Systematic Reviews of Interventions.[36] A third reviewer will be consulted in case of disagreement (ASiebenhofer). Additionally, the reporting quality of exercise interventions in individual studies will be assessed using the CERT.[37] Quality of evidence for every outcome will be evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[38 39]

Data synthesis

A quantitative synthesis will only be conducted if studies are homogeneous enough for effect sizes to be pooled. Statistical analyses will be performed in accordance with the recommendations of the latest version of the Cochrane Handbook and will be performed using R software. Given the differences in study population and treatment design, both within-study variation and variation in the true effect between studies may have to be accounted for statistically by applying a random-effects model. For continuous variables, reported final mean values will be extracted for both the intervention group and the CG, along with group sizes and their SD. We intend to compute weighted raw mean differences as effect sizes expressed with 95% CIs in all meta-analyses and consequently to pool only those studies that use the same outcome scales. SD will be back calculated from reported CIs following recommendations in the Cochrane Handbook.[36] However, we will ensure that all scales point in the same direction. For binary outcome variables, results will be described in terms of relative risk or ORs calculated with 95% CIs. Data from cross-over trials may either be pooled separately or combined with parallel group trials, depending on the data that is available.[40] In addition to standard heterogeneity statistics, the visual analysis of forest plots will be used to identify heterogeneity. Funnel plots will be used to assess reporting bias. In order to synthesise effect measures from parallel, cluster and cross-over RCTs, we may use approximate approaches to calculate effect measures of the individual studies for the meta-analysis as detailed in chapter 23 of the Cochrane Handbook.[36]

Where quantitative analysis is not applicable, data will be represented in tabular form and synthesised narratively. Data from secondary research objectives will be summarised using basic descriptive statistics, frequency analysis for metric data and descriptive narration for nominal data.

Planned sensitivity and subgroup analysis

If considered useful, the following subgroup analyses will be conducted to examine whether variations in intervention and population characteristics influenced the results:

- Based on exercise stimuli: that is, multicomponent exercise interventions only, group-based exercise interventions only, high volume exercise interventions only (session duration×frequency×programme), high-intensity exercise interventions only (ie, VO_2 max and Heart rate reserve >60%, HR max >75%, Borg scale >14).
- Based on the patient population: that is, mean age, mean MMSE, gender, MCI subtype, global region and previously sedentary adults.
- Based on studies that adhere to CERT reporting standards.

ETHICS AND DISSEMINATION

To the best of our knowledge, this is the first systematic review to evaluate long-term patient-relevant, cognitive and non-cognitive effects of physical activity and exercise interventions in MCI populations.

This work will not only inform professionals in primary care about the effectiveness of physical activity and exercise interventions. It will also support them to make recommendations of physical activity and exercise based on evidence with a high standard of reporting intervention details as we appraise both information detail of physical activity and exercise interventions and internal validity.

Timeline for the review

At the time of submission, we will already have started screening full-text screening. This systematic review is scheduled to end in August 2022.

Patient and public involvement

We plan to recruit people living with MCI for participation in a workshop by the help of the Frankfurter Forum für Interdisziplinäre Alternsforschung (FFIA/Center of Interdisciplinary Aging Research) at Goethe University Frankfurt and Alzheimer Gesellschaft Hessen e.V. (Alzheimer Society Hessen) parallel to performing searches and screening. In this workshop, we will ask people living with MCI to rank what they perceive to be meaningful endpoints to be included in research generally and this systematic review specifically.

Dissemination

The results will be disseminated through peer-reviewed journals and local and international conferences. Dissemination to lay audiences and gate-keeping addressees will be piloted by creating a patient-friendly video abstract to be disseminated through appropriate (social media) channels. Alzheimer Society Hessen will support the dissemination of the video abstract within its network.

Research data management

In accordance with Goethe University's policy on research data management, all datasets generated during this study will be made available in the open access repository Zenodo (10.5281/zenodo.5589277) and will comply with the FAIR principles (findable, accessible, interoperable, reusable).[41]

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Contributors AIG-G and MD wrote the initial draft of the protocol. ASiebenhofer is the guarantor of the review. KJ assisted in the identification of databases and reviewed the search strategy. WB, AB, ASchall, VAT, JP and ASiebenhofer are co-supervisors of this project, provided advice throughout the development of the protocol and contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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