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Modifiable enablers and barriers of exercise adherence in older adults with MCI/dementia using the Theoretical Domains Framework: a systematic review protocol

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ABSTRACT

Introduction Considering the inefficiency of pharmacological intervention, exercise as one of the non-pharmacological interventions is recommended for older adults with MCI/dementia and its effects have been proven by practice. However, the positive effects of all exercise interventions depend highly on exercise adherence. In fact, exercise adherence is not ideal from the results of previous literature among older adults with MCI/dementia. High drop-out rates reduce the effect of exercise for MCI and dementia. Allowing for the current studies on exercise adherence in older adults with MCI/dementia still have some deficiencies. The aim of this paper is to identify the modifiable barriers and enablers of exercise adherence in older adults with MCI/dementia from the perspectives of patients, carers and healthcare

professionals according to Theoretical Domains Framework(TDF) of a broad based theoretical framework for behaviour change in order to provide references for healthcare professionals developing exercise strategies and improving exercise adherence.

Methods and analysis A systematic review of qualitative and quantitative studies will be conducted. PubMed, Embase, The Cochrane Library (Cochrane Central Register of Controlled Trials), Web of Science(Science and Social Science Citation Index), China National Knowledge Infrastructure(CNKI), the Wan Fang Database and grey literature will be searched and two reviewers will screen studies according to predefined eligible criteria. Barriers and enablers will be extracted and synthesised on the basis of the Theoretical Domains Framework from perspectives of patients, carers and healthcare professionals by two independent reviewers.

Ethics and dissemination We will report this review in accordance with the PRISMA statement. This systematic review does not require ethical approval as no primary data are collected. We are going to publish our findings in a peer-reviewed journal.

PROSPERO registration number CRD42019117725.

Strengths and limitations of this study

1.To the best of our knowledge, no previous work has been carried out to systematically map and categorise modifiable enablers and barriers of exercise adherence in older adults with MCI/dementia using the Theoretical Domains Framework.

2.Our systematic review will be the first attempt to summarise the current available evidence on the insights of patients, carers and healthcare professionals.

3.We will perform an all-round search of published and grey literature with no restrictions on date, language or geographical location.

4.The main study limitation is that no meta-analysis or other statistical analysis will be performed in this review.

BACKGROUND

Description of the MCI/dementia condition

Mild cognitive impairment(MCI) is the intermediate phase between normal cognitive functioning and dementia, characterized by cognitive decline that is larger than expected considering a person's age and education, though without conspicuous interference in

daily-life activities.[1] The published prevalence of people with MCI is approximately 10% to 20% worldwide that depends on the sample and the follow-up duration of studies at present.[2] People with MCI have a heightened risk of further cognitive decline and progression to dementia, it is reported that 10% to 15%, 60.5%, and 100% of patients with MCI will develop full dementia within 1 year, 5 years, and 9.5 years, respectively, after initial diagnosis of MCI.[3] Dementia is characterized by progressive and severe cognitive decline, motor deficits and/or behavioral problems causing a decline in activities of daily living (ADL).[4] As life expectancy is getting longer worldwide, the number of people affected by MCI and dementia is steadily growing.[5] According to estimates from the World Alzheimer Report, The number of people with dementia is expected to dramatically increase in the coming decades, from 47 million in 2015 to 131.5 million by 2050.[6] These rapidly growing numbers will have a tremendous social impact, placing a high economic burden on the healthcare system.[6-7] Therefore, the World Health Organization(WHO) stresses to take global action against cognitive decline and dementia, encouraging governments all over the world to focus on prevention, disease modifying therapies and improving health care services.[8]

Pharmacological and nonpharmacological interventions are two promising options for MCI and dementia. To date, there are no definite or disease-modifying therapeutic options for dementia, only the cholinesterase inhibitors, galantamine, rivastigmine, donepezil and the N-methyl D-aspartate receptor antagonist memantine are approved for the symptomatic therapy of cognitive symptoms in dementia so far.[9-10] These drugs may initially improve cognition and slow down the clinical progression of dementia but are not capable of stopping the underlying pathological process of dementia, including amyloid accumulation, tau protein aggregation, synaptic loss and neuronal death.[10-11] In the clinical use of drug, there still exist uncertainties, for example, on their efficacy in early stages of dementia or the MCI-dementia phase, when to stop them or how to monitor long-term efficacy in the individual patient and long-term medication costs a large sum of money which exerts a big burden on families and the whole society.[10]

For the treatment of MCI, as far as diagnostic uncertainty and the heterogeneous underlying pathophysiological mechanisms are concerned, only limited therapies are currently available.[12] There isn't any approved pharmacological treatment exist for MCI so

far and only modest evidence for symptomatic treatment efficacy.[13] Most results reflect not only a lack of effectiveness of drug therapy but also have a negligible effect on the cognition of people with MCI, for example, the cholinesterase inhibitors galantamine, this medication increases the rate of death and has no effect on the conversion rate from MCI to dementia.[12-14] And pharmacotherapy is preferably limited to the patients with MCI who are at higher risk of transition to dementia.[15-16] Factors including limited options, medications side-effects, uncertain prognosis, and inappropriate social, psychological, more economic spending and ethical consequences restrict the pharmacological treatment of MCI.[16] Therefore, there is an urgent need for more other effective treatment options for cognitive symptoms. Many researches are focusing on non-pharmacological interventions that mainly include cognitive intervention, exercise, music therapy, psychological intervention and diet management, and etc.[17-18] A series of studies have examined the effects of non-pharmacological interventions on cognition in older adults with MCI/dementia, including memory, abstraction, mental flexibility, self-control, executive functions and attention, which were measured by validated and reliable instruments.[18-19] Non-pharmacological interventions have less risk than pharmacological interventions(i.e. low likelihood of contraindications or problems that occur with polypharmacy).[18] In this occasion, older adults may prefer non-pharmacological interventions to maintain cognitive function rather than pharmacological strategies with possible side effects.

As one of the major recommendations for non-pharmaceutical interventions, exercise has been consistently found to be associated with a reduced risk of developing dementia(regardless of its subtype)/MCI as shown in several systematic reviews and meta-analyses, which also reports exercise places a positive effect on physical, cognitive, functional, and behavioral outcomes for MCI and dementia.[20-22] Such improvements might directly enable the person to perform daily activities including independent self-care or with little assistance.

Despite these positive findings, there remain concerns that older adults with MCI/dementia are physically inactive and their adherence to exercise is poor.[23-24] Tak et al showed that maintenance of participation in exercise programs in older adults with MCI is low, only 25% continued exercising after the end of the 12-month RCT. [24] And only 19% of

67 nursing home AD residents had high adherence to a year-long exercise program (completed > two-thirds of possible exercise sessions), and 52% had low adherence(completed < one third of possible sessions), mean adherence was 33.2±25.5% in the whole sessions was found in Rolland's study.[23] A randomized controlled trial conducted by Suttanon et al showed similar results that forty older adults with mild to moderate Alzheimer's disease were randomized to a six-month home-based individually tailored balance, strengthening and walking exercise programme or a six-month home-based education programme(control), only fifty-eight percent of the exercise group finished the programme.[25] Thus it can be seen that the level of adherence of older adults with MCI/dementia is still not optimistic about the current situation and we need to pay more attention on relevant research of exercise adherence.

Why is it important to do this review?

The positive effects of all exercise interventions depend highly on exercise adherence.[26] High drop-out rates reduce the effect of exercise for MCI and dementia. Lowery D et al also concluded that it is an essential research to identify factors influencing participation in exercise in community dwelling adults with dementia for the reason that they found that only 30.7% achieved the prescribed frequency of the exercise intervention after they went on a randomized control trial.[27] In order to increase MCI/dementia patients' exercise adherence levels, there is a need to understand better the factors that affect exercise adherence in such populations. Specifically, identifying the barriers and enablers of exercise may improve the success rate of exercise implement suitable for dementia patients' care. Stubbs et al have systematically reviewed the literature to establish the factors associated with exercise participation in community dwelling adults with dementia, they find that increased energy intake, resting metabolic rate, fat free mass, gait speed, global motor function, overall health related quality of life (HRQOL), physical HRQOL, higher levels of social functioning and reduced apathy were positively associated with exercise; and taking≥ four medications, dizziness, lower ADL function, a history of falls, less waking hours in the day, more autonomic problems and delirium were negatively associated with PA.[28] A more recent meta-analysis further collected and synthesized the evidence on known barriers and enablers to adherence of institutionalized older people living with dementia to group exercise,

including three thematic categories, bio-medical reasons and mental wellbeing and physical ability; relationship dynamics; and socioeconomic reasons.[29]

However, the current studies on exercise adherence in older adults with MCI/dementia still have the following deficiencies:

(1) The lack of theory framework

Previous studies on enablers and barriers of exercise adherence in older adults with MCI/dementia lacked the support or elaboration of behavioral theory framework. Behavioral theory provides alongside potential determinants (or constructs)—a structure and context for thinking logically about these determinants and their relationships.[30] Applying a behavioral theoretical framework to assessing barriers and enablers can effectively help develop tailored informed strategies to support the effective implementation of evidence-based practices.[31] In this study, we will rely on Theoretical Domains Framework(TDF) to classify enablers and barriers of exercise adherence in older adults with MCI/dementia. The TDF is a comprehensive framework that synthesizes a number of behavior change theories. It was first developed in 2005 with 12 domains and 128 constructs, and in 2012, its validity was reevaluated, and a refined version of the TDF was proposed with 14 domains and 84 constructs.[32-33] TDF has been successfully used in many medical systems for clinical performance improvement to explain practical issues and provide theory-informed guide for further effective interventions.[34-36] The TDF therefore offers an appropriate theory to support an evidence synthesis of drivers of adherence which can be used to facilitate the design and development of targeted exercise interventions.

(2) Little know about the barriers and enablers to targeted exercise amongst older adults with MCI

MCI and dementia are two different stages of the cognitive impairment disease. The psychosocial characteristics of the patients may exist differences in exercise adherence theoretically. To the best of our knowledge, the factors associated with exercise adherence of older adults with MCI only are reported by a small number of clinical studies, and no author has systematically reviewed the related factors.[24]

(3) The lack of systematic research on the modifiable factors that impact exercise adherence in older adults with MCI/dementia

We cannot change behavior of exercise adherence resulting from nonmodifiable factors such as family history, sex and age. Identification of such modifiable factors and assessing which factors improve or deteriorate exercise adherence is a vital approach to designing interventions. This information would serve as a reminder that provides guidance for medical staff refining target population and intervention methods in theory and then contributing to the development of adherence-oriented programmes of exercise intervention in practice.

(4) The absence of research on discussing adherence from different people's insights

The insights of patients, carers and healthcare professionals often differ regarding the barriers and enablers of exercise adherence due to differing priorities and knowledge of the situation.[37-39] "Carers" are used to refer to the primary carer for someone diagnosed with MCI/dementia, the family members of patients or hired the nursing staff are both included, they are primarily responsible for patients' food and accommodation and may have a better understanding of living environment factors of patients.[38] Older adults especially with dementia often need help from their carers to complete many of their daily activities, it is expected that carers would play an important role in exercise intervention.[39] Therefore, opinions from carers should taken into account. Healthcare professionals include physicians, nurses, clinical psychologists, the manager or administrator of nursing home, experts in exercise intervention, etc.[37, 40] They are mainly in charge of the whole exercise intervention program who may pay more attention to the methodological factors of exercise, and previous studies also have highlighted the importance of support from health professionals to encourage people to take part in an exercise program.[41-42] Currently the barriers and enablers of exercise adherence among older adults with MCI/dementia from different people's perspectives have not been studied, so that the information about the barriers and enablers may lack for more comprehensive information which will not be good for generate more generalisable theories.

All those discussed above show that an overall understanding of the modifiable barriers and enablers to exercise intervention from the perspectives of patients, carers and healthcare professionals, synthesised according to TDF of a broad based theoretical framework for behaviour change, is needed. Thus we aim to conduct a systematic review to collect and synthesize the available evidence on modifiable barriers and enablers of exercise adherence

among older adults with MCI/dementia, and further classify them into the domains of the TDF to inform clinical practice of healthcare professionals recommending and prescribing exercise, and to develop strategies that promote the behavior change needed in patients for long-term exercise adherence.

METHODS/DESIGN

This protocol is written in accordance with the recommendation of the PRISMA-P Elaboration and Explanation document.[43] We plan to complete the systematic review with an expected completion date of May 31, 2020, This review has been registered with the international database of prospectively registered systematic reviews in health and social care(PROSPERO; registration number CRD42019117725).

Eligibility criteria

Types of participants

Eligible studies will include any type of MCI/dementia. No limitations will be placed on the severity of MCI/dementia, length of time since diagnosis. No restrictions will be placed on severity of depression, anxiety, psychological distress or mental health-related quality of life. These individuals will be included as follows:

(1) The people aged 65 years or older.

(2) For dementia: Including studies involving people diagnosed with any type of dementia, according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition(DSM-3), Fourth Edition(DSM-4), Text Revision(DSMIV-TR), or Fifth Edition(DSM-5), International Classification of Diseases, Tenth Revision(ICD-10), Mini Mental State Examination(MMSE)/Montreal Cognitive Assessment(MOCA) score available, or other alternative validated diagnostic criteria, or recorded in medical records.

(3) For MCI: Including studies involving people diagnosed with any type of MCI according to the criteria in the DSM-5 criteria, Petersen's criteria, alternative validated diagnostic criteria, MMSE/MOCA score available, or where recorded in medical records.

(4) These will be excluded: Patients who have severe visual or auditory impairment, serious medical conditions in major organs(heart, lung or kidney), illnesses affecting mobility or are unable to accept assessments or interventions that are required in this study for any reasons.

Types of exercise intervention

This systematic review will include all studies involving any type of exercise. Exercise intervention is defined as a type of physical activity that is planned, structured and repeated over a period of time.[44] The eligible exercise can be categorized into resistance training, aerobic exercise, combined exercise and other types of training. In addition, all organizational forms of intervention(individual, group, or mixed) are eligible for inclusion. And supportive strategies(face to face, telephone, email) will be eligible for inclusion. There will be no limitations about the professional background of the person sustaining the exercise intervention, additionally unsustained(self-guided/self-administered) interventions will also be eligible for inclusion.

Type of setting

Studies in any setting where exercise intervention is conducted including healthcare institutions, community, home or in any geographical setting globally will be considered for inclusion.

Types of outcome measures

Outcomes of studies that report barriers and enablers influencing uptake and/or maintenance of exercise in older adults with MCI/dementia will be included.

Types of studies

The searches are not limited to specific study design. Hence, all study designs using qualitative or quantitative methodologies will be included in the review. The papers will be categorized by study design using the following categories: randomized-controlled trial, quasi-controlled trial, cohort study, cross-sectional study, and qualitative study.

Theme of studies

Studies will be included if

(1) They directly explore the factors/barriers/enablers/motivation that correspond to engagement in exercise;

(2) They directly address or focus on any aspect of the experience or perceptions of older adults with MCI/dementia regarding exercise and mentioning exercise adherence enough to answer our question.

The language of studies

Studies will be no language restrictions.

Publication year

From 1 January 1990 to the date of the searches.

Information sources

The following electronic bibliographic databases: PubMed, Embase, The Cochrane Library, Web of Science, China National Knowledge Infrastructure(CNKI), and the Wan Fang Database will be searched from 1 January 1990 to the date of the searches about Human studies. In order to improve the completeness of the literature, grey literature sources will be considered. We will further check the reference list of the included studies and relevant reviews.

Search strategy

Based on key terms from previous literature reviews and Medical Subject Headings, Our search will use both the medical subject headings and text word and will combine concepts for the influencing factors of adherence, Our search strategy will consist of three parameters: disease(MCI/dementia), intervention(exercise) and outcome(adherence). The search strategy we will use for the retrieval of reports of trials from PubMed is summarized in Table 1. The search strategy will be modified as necessary for other databases.

Table 1 **The search strategy of PubMed**

Number	Search items
1	Dementia OR Cognitive Dysfunction OR Mild Cognitive Impairment* OR MCI OR VCI OR AAMI OR SMC OR ACMI OR ARCD OR CIND OR (nMCI or aMCI or mMCI or MCIa) OR MCD OR AACD OR MNCD OR Mild Neurocognitive Disorder* OR cogn* OR Cognitive impairment OR Alzheimer OR AD OR Alzheimer's disease
2	Ageing OR aging OR Elderly OR "Aged,80 and over" OR "Old* age*" OR "middle age*" OR "old* adults" OR senior* OR senior citizens OR old people OR old person
3	Exercise OR Physical activit* OR Treadmill training OR Balance OR Strength OR Endurance OR Attention training sport* OR jogging OR physical therapy OR physiotherapy OR exercise* OR fitness OR rehabilitation OR flexibility OR motor activit* OR leisure activit* OR strength OR balance OR aerobic* OR physical* OR

	training OR bicycling OR cycling OR swim* OR gym* OR walk* OR danc* OR yoga OR joga OR tai chi OR tai ji OR taichi OR Taijiquan OR tai-chi OR pilates OR movement OR recovery of function OR inactivit* OR sedentary OR physical inactivit* OR occupational therapy OR physical stimulation OR physical education OR physical medicine OR resistance OR mind-body OR Mind Body
4	barrier* OR enabler* OR motivators OR facilitators OR implementation OR adherence OR compliance OR support OR selfefficacy OR self-efficacy OR self efficacy OR self-efficiency OR motivation OR experience* OR perspective* OR factor* OR attendance OR predictor*OR preference*
5	1 and 2 and 3 and 4

The selection process of studies

The study selection process will be reported according to the PRISMA flowchart.[45] First, removing duplicates using the reference manager software Endnote X7. Then titles and abstracts of articles will be screened, selected full-text articles will be assessed for eligibility and data will be extracted by two independent researchers(HY and YX C), disagreement will be solved by discussion. A third researcher (CX G) will be invited in case of persistent contradiction. In the final, two other authors (HQ C and JW) will assess potentially eligible full-text studies to make sure if they meet the criteria set for inclusion.

Data items and data abstraction process

All data will be extracted into an Excel file. Data extraction will be undertaken independently by two researchers(XT Z and LN W). Any disagreement between the two researchers will be resolved through further discussion and adjudication by a third reviewer(J W). For each study that meet the inclusion criteria, It is anticipated that we will extract the following information:

(1) Bibliographic information: the journal name, title, first author's name, publication year, language of the study, country of corresponding author;

(2) Study design: specific type of study, exercise intervention technique, duration, outcomes measured, instruments used to measure them, data collection methods, sample size, quality of

study.

(3) Participants data: type of disease, disease screening tools/diagnostic tools, setting, inclusion and exclusion criteria, sample size, sociodemographic characteristics(eg. age, ethnicity, country).

(4) Outcomes: definition and rate of adherence, influencing factors of adherence.

Risk of bias (quality) assessment and meta-bias

Two independent reviewers rigorously will assess the quality of each paper. The Newcastle-Ottawa Scale (NOS) will be used to assess the quality of cohort articles.[46] Cross-sectional studies will be examined using the Agency for Healthcare Research and Quality (AHRQ).[47] Randomized controlled trials will be assessed according to PEDpro.[48] The Joanna Briggs Institute (JBI) critical appraisal checklist will be used to assess the quality of quasi-randomized controlled trials.[49] Qualitative research will adopt the tool that JBI made critical appraisal tools for qualitative research in 2016.[50]

Data synthesis and analysis

This review will synthesize all related qualitative and quantitative literature. Characteristics and outcomes of each study will be summarized and presented in an evidence table. We will use the statistical software package NVivo V.12 to help us manage the extract useful information and we will classify three themes from the perspective of the patient perspective, carers perspective and healthcare professional perspective to conform the aim of our study. We will divide each subject theme into two subthemes(modified barriers and enablers), and for each subtheme we will create 15 domains(14 TDF domains plus 'Others'). Then, the identified information from every article will be classified into the fourteen subcomponents of the TDF plus 'Others'. The whole process of date synthesis will be conducted by one researcher(XT Z) and checked by a second independent researcher with experience in the thematic analysis(HQ C) to enhance credibility.

DISCUSSION

This systematic review will be the first try that map modifiable barriers and enablers to exercise for older adults with MCI/dementia to the domains of the TDF. There are three major advantages of adopting TDF, and they are as follows:

First of all, in theory, TDF is a comprehensive framework that synthesizes many behavior

change theories, which lower the risks of missing relevant theoretical constructs or including irrelevant ones, so it can be used for summarizing the related factors of exercise adherence reported in the literature from all angles. The next, from a practical point of view, the constructs comprising the TDF provide a basis from which to create an understanding of the behaviours associated with adherence of exercise and help clinical staff make appropriate improvement strategies to facilitate behaviour change for exercise adherence.[33] Last but not the least, the usefulness of TDF has been confirmed in various medical practice gradually. In Denmark, TDF has been applied into understanding factors influencing behavior in the implementation of tobacco cessation programmes and counselling guidelines amongst dental providers.[34] In Canada, it has been applied into assessing barriers to change for planning health care quality interventions.[35] In Australia, TDF has been applied into identifying what are the barriers and enablers of referral, uptake, attendance and completion of pulmonary rehabilitation for people with chronic obstructive pulmonary disease (COPD) and the results provides a framework for identifying target areas for intervention.[36] In view of the effectiveness of TDF, it therefore offers an appropriate theory to synthesize extensive barriers and enablers reported in single studies and provide a deeper insight of the influences on evidence-based behavior change means. Findings based on the theory can be used to inform the development of effective adherence interventions to assist practitioners in choosing the most suitable evidence-based exercise programs in clinical settings accordingly.

In addition, this review will synthesise and report qualitative and quantitative data about exercise adherence from the perspective of patients, carers and healthcare professional. The results will help understand common influencing factors to focus on how to modify barriers best and enhance enablers to increase the use and appeal of the exercise intervention. And it will facilitate effective access to care and treatment to help people with MCI/dementia have a wider adoption to exercise intervention. In the meantime, it would have substantial implications for researchers, clinicians, and policymakers about how to provide a better, specialist care for older adults with MCI/dementia.

Amendments

If we need to amend this protocol, the date of each amendment will be accompanied by a description of the change and the rationale.

Patient and public involvement

Patients and public were not involved at this stage of the project.

Ethical issues

The systematic review is a retrospective study, using data that are publicly available. As no primary data collection will be undertaken and does not require a formal ethical assessment and no informed consent are needed.

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Conflict of interest

All authors declare that we have no conflicts of interest.

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Contributors

All authors contributed to the development of the study design and search strategy. XT Z and LN W designed the study and wrote the protocol. XT Z and H Y wrote the search strategy. H Y, YX C and CX G screened the literature. WJ and HQ C checked selected article. All authors provided feedback and approved the final protocol.

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Reporting checklist for protocol of a systematic review.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a not an update
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	20
Amendments			
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Support			

Sources	#5a	Indicate sources of financial or other support for the review	n/a not included
Sponsor	#5b	Provide name for the review funder and / or sponsor	20
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	20
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-11
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	11
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	12
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	14
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	15
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	17
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	16
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	17
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	16
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	17
Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of individual studies,	17

individual studies		including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	n/a no meta-analysis or other statistical analysis
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's T)	n/a no meta-analysis or other statistical analysis
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a no meta-analysis or other statistical analysis
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	20
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a no meta-analysis or other statistical analysis
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a

Notes:

- 1b: n/a not an update
- 5a: n/a not included
- 15a: n/a no meta-analysis or other statistical analysis
- 15b: n/a no meta-analysis or other statistical analysis
- 15c: n/a no meta-analysis or other statistical analysis
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Modifiable enablers and barriers of exercise adherence in older adults with MCI/dementia using the Theoretical Domains Framework: a systematic review protocol

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Modifiable enablers and barriers of exercise adherence in older adults with MCI/dementia using the Theoretical Domains Framework: a systematic review protocol

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Modifiable enablers and barriers of exercise adherence in older adults with MCI/dementia using the Theoretical Domains Framework: a systematic review protocol

ABSTRACT

Introduction As one of the non-pharmacological interventions, exercise has a good effect on older adults with mild cognitive impairment (MCI)/dementia. Exercise adherence is not ideal among older adults with MCI/dementia at present. Allowing for the current studies on exercise adherence in older adults with MCI/dementia still have some deficiencies. The aim of this paper is to: (1) identify the modifiable barriers and enablers of exercise adherence in older adults with MCI/dementia from the perspectives of patients, caregivers and healthcare professionals. (2) use the Theoretical Domains Framework (TDF) to organize the identified factors of exercise adherence among included studies.

Methods and analysis A systematic review will be developed including qualitative and quantitative studies. PubMed, Embase, The Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), the Wan Fang Database and grey literature will be searched between January 1990 and February 2020. We will identify peer-reviewed publications which examined enablers and barriers of exercise adherence. Searches will no limitation in language publications using search terms related to exercise interventions, adherence and dementia/MCI. Titles, abstracts and full-text papers will be screened by two independent reviewers according to the predetermined inclusion and exclusion criteria. We will use the statistical software Nvivo.12 to manage the information. The Theoretical Domains Framework will be used as an a priori 'framework' to synthesize extracted information in this study. We will map the literature identified modifiable barriers and enablers to the domains of TDF.

Ethics and dissemination This review will summarize modifiable enablers and barriers of exercise adherence in older adults with MCI/dementia for the first time. Ethical approval is not required as no primary data are collected. We are going to disseminate our findings to the scientific and medical community in peer-reviewed journals. The review findings will facilitate effective access to care and treatment to help older adults with MCI/dementia have a

broader adoption to exercise.

PROSPERO registration number CRD42019117725

Strengths and limitations of this study

1. To the best of our knowledge, previous work didn't systematically map and categorize modifiable enablers and barriers of exercise adherence about older adults with MCI/dementia using the Theoretical Domains Framework.
2. Our systematic review will be the first attempt to summarize the currently available evidence on the insights of patients, caregivers and health care professionals.
3. We will perform an all-round search of published and grey literature with no restrictions on language and geographical location.
4. The main limitation of the study is that no meta-analysis or other statistical analysis will be performed in this review.

BACKGROUND

Description of the MCI/dementia condition

Mild Cognitive Impairment (MCI) is the intermediate phase between normal cognitive function and dementia, characterized by a delay in cognitive decline that is larger than expected considering a person's age and education, though without marked interference in daily-life activities.[1] The published prevalence of people with MCI is approximately 10% to 20% worldwide depending on the sample and the follow-up duration of studies.[2] People with MCI have a heightened risk of further cognitive decline and progression to dementia. It is reported that 10% to 15%, 60.5%, and 100% of people with MCI may develop full dementia within 1 year, 5 years, and 9.5 years, respectively, after initial diagnosis of MCI.[3] Dementia is characterized by progressive and severe cognitive decline, motor deficits with or without behavioural problems causing a decrease in activities of daily living (ADL).[4] As life expectancy is getting longer worldwide, the number of people affected by MCI and dementia is steadily growing.[5] According to estimates from the World Alzheimer Report, the number of people with dementia will dramatically increase in the coming decades, from 47 million in 2015 to 131.5 million by 2050.[6] These rapidly growing numbers will have a tremendous social impact, placing a high economic burden on the healthcare system.[6-7]

To date, there are no definite or disease-modifying therapeutic options for dementia and MCI. For the pharmacological interventions of dementia and MCI, these drugs may initially improve cognition and slow down the clinical progression of dementia/MCI but are not capable of stopping the underlying pathological process of disease, including amyloid accumulation, tau protein aggregation, synaptic loss and neuronal death.[8-9] Besides, there are uncertainties concerning the use of these medications, for example, on their efficacy in early stages of dementia or the MCI-dementia phase, when to stop them or how to monitor long-term effectiveness in the individual older adults with MCI/dementia.[8] Because of this, many researchers are focusing on non-pharmacological interventions. As one of the significant recommendations for non-pharmaceutical interventions, exercise has been proved to be associated with a reduced risk of developing MCI/dementia. Exercise (aerobic training, resistance training and mind-body exercise, etc.) is a promising strategy for preventing or delaying cognitive decline, and its salutary effects on cognitive function have been demonstrated in animal models and in a growing number of clinical studies of older adults with MCI/dementia.[10-12]

Despite these positive findings, there remain concerns that older adults with MCI/dementia are physically inactive and their adherence to exercise is poor.[13-14] Tak et al. showed that maintenance of participation in exercise programs in older adults with MCI is low, only 25% continued applying after the end of the 12-month randomized controlled trial (RCT).[14] It was found in Rolland's study that 19% of the individual with dementia completed more than two-thirds possible exercise sessions in a year-long trail.[13] 52% of participants just completed less than one-third of possible practices, mean adherence was 33.2±25.5% in the whole sessions.[13] Thus it can be seen that the level of exercise adherence of older adults with MCI/dementia was still not optimistic about the situation of adherence and we would need more attention on relevant researches of exercise adherence.

The significance for doing this review

The positive effects of all exercise interventions depend highly on exercise adherence.[15] Lowery D et al. also conclude that it is essential to identify factors influencing the participation among older adults with dementia in the community since only 30.7%

participants have achieved the prescribed frequency of the exercise in their research.[16] In order to increase exercise adherence levels of older adults with MCI/dementia, there is a need to understand better the factors that affect exercise adherence in such populations. Specifically, identifying the barriers and enablers of exercise is beneficial to improve the success rate of exercise implement which will promote the rehabilitation for older adults with dementia. Some previous studies have established the factors associated with exercise participation in community-dwelling adults with dementia, including increased energy intake, resting metabolic rate, fat-free mass, gait speed, taking≥ four medications, dizziness, lower ADL function, a history of falls, delirium and so on.[17-18]

However, the current studies on exercise adherence in older adults with MCI/dementia still have the following deficiencies:

(1) The absence of research on discussing adherence from different people's insights

The insights of patients, caregivers and health care professionals often differ regarding the barriers and enablers of exercise adherence due to differing priorities and knowledge of the situation.[19-26] For patients, the complicacy of symptoms can make it more difficult for older adults with MCI/dementia to participate in exercise programs. Older adults with dementia/MCI can usually express their views and preferences about what is important to them when exercising and it is morally and ethically necessary to consider those views.[19-20] In comparison to caring for older adults with normal cognitive function, those caregivers taking care of older adults with MCI/dementia face a substantially higher burden due to changes that are typically associated with dementia.[21-22] Relatively little is known on how caregivers of older adults with MCI/dementia manage their support arrangements, which strategies they follow and which structures are perceived as helpful or obstructive in exercise.[22-23] Therefore, opinions from caregivers should be taken into account. Furthermore, previous studies also highlighted the importance of support from health care professionals to encourage older adults with MCI/dementia to take part in exercise.[24-25] The research has shown that participants' adherence to exercise is improved when the instructions they receive are specific and understandable from health care professionals.[26] In the meantime, many health care professionals were also concerned about participants' ability to access exercise programs.[14,25]

Caregivers may be a bridge to follow the advice from health care professionals and to supervise older adults with MCI/dementia exercise better. Teamwork and collaboration to improve exercise adherence among patients, caregivers and health care professionals become paramount. These findings can inform future interventions to make them more meaningful for this population. Currently, the barriers and enablers of exercise adherence among older adults with MCI/dementia from different people's perspectives have not been studied.

(2) The lack of theory framework

Previous studies on enablers and barriers of exercise adherence in older adults with MCI/dementia lacked the support or elaboration of behavioural theory framework. Behavioural theory can provide potential determinants and a corresponding structure for thinking logically about these determinants and their relationships.[27] Applying a behavioural theoretical framework for assessing barriers and enablers can effectively help develop tailored informed strategies to support the effective implementation of evidence-based practices.[28] In this study, we will rely on Theoretical Domains Framework (TDF) to classify enablers and barriers of exercise adherence in older adults with MCI/dementia. The TDF is a comprehensive framework that synthesizes many behaviour change theories. It was first developed in 2005 with 12 domains and 128 constructs, and its validity was reevaluated in 2012 with a refined version including 14 domains and 84 constructs.[29-30] This framework offers an appropriate structure for supporting an evidence synthesis of barriers and enablers as it will help these factors to be linked to evidence-based behaviour change techniques. The TDF has been successfully used in many medical systems to assess barriers and facilitators about practical issues and provide a theory-informed guide for further effective interventions.[31-33] Therefore, the constructs of TDF may provide a basis to help to understand the barriers and facilitators of exercise adherence of older adults with MCI/dementia.

(3)The lack of systematic research on the modifiable factors that impact exercise adherence in older adults with MCI/dementia

It is recognized that the barriers and enablers to targeted exercise amongst older adults with MCI/dementia are multifactorial.[14-18] Furthermore, these factors are partly unmodifiable or unavoidable that is difficult for us to change (e.g. family history, sex and age). Identification

of such modifiable factors and assessing which factors improve or deteriorate exercise adherence is a vital approach to design interventions. This information would serve as a reminder that guides medical staff in refining target population and intervention methods theoretically and then contributing to the development of adherence-oriented programs in practice. Therefore, we first attempt to identify primary research findings of modifiable barriers and enablers that may help to design target interventions to improve their overall effectiveness.

As summarized in the above, they all show that an overall understanding of the modifiable barriers and enablers to exercise intervention from the perspectives of patients, caregivers and healthcare professionals, synthesized according to a broad-based theoretical framework for behaviour change, is needed. Thus we aim to conduct a systematic review to collect and synthesize the available evidence on modifiable barriers and enablers of exercise adherence among older adults with MCI/dementia. Then we can further classify them into the domains of the TDF to inform clinical practise for recommending and prescribing exercise and to develop strategies for long-term exercise adherence.

METHODS/DESIGN

This protocol is written following the recommendation of the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P).[34] We plan to complete the systematic review with an expected completion date of October 31, 2020. This review has been registered with the international database of prospectively registered systematic reviews in health and social care (PROSPERO; registration number CRD42019117725).

Eligibility criteria

Types of participants

Eligible studies will include any type of MCI/dementia. No limitations will be placed on the severity of MCI/dementia, length of time since diagnosis. No restrictions will be placed on the severity of depression, anxiety, psychological distress or mental health-related quality of life. These individuals will be included as follows:

(1) The people aged 65 years or older.

(2) For dementia: Including studies involving people diagnosed with any type of dementia,

according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-3), Fourth Edition (DSM-4), Text Revision (DSMIV-TR), Fifth Edition (DSM-5), International Classification of Diseases, Tenth Revision (ICD-10), Mini-Mental State Examination (MMSE)/Montreal Cognitive Assessment (MOCA) score available, other alternative validated diagnostic criteria or recorded in medical records.

(3) For MCI: Including studies involving people diagnosed with any type of MCI according to the criteria in the DSM-5 criteria, Petersen's criteria, an alternative validated diagnostic criteria, MMSE/MOCA score available, or where recorded in medical records.

(4) These will be excluded: Patients who have a severe visual or auditory impairment, serious medical conditions in major organs (heart, lung or kidney), illnesses affecting mobility or are unable to accept assessments or interventions that are required in this study for any reasons.

Types of exercise intervention

This systematic review will include all studies involving any type of exercise. Exercise intervention is defined as a type of physical activity that is planned, structured and repeated over a period of time.[35] The eligible exercise can be categorized into resistance training, aerobic exercise, combined exercise and other types of training. In addition, all organizational forms of intervention (individual, group, or mixed) are eligible for inclusion. Besides, supportive strategies (face to face, telephone, email) will be eligible for inclusion. There will be no limitations about the professional background of the person sustaining the exercise interventions, additionally unsustained (self-guided/self-administered) interventions will also be eligible for inclusion.

Type of setting

Studies in any setting where exercise intervention is conducted including healthcare institutions, community, home or in any geographical setting globally will be considered for inclusion.

Types of outcome measures

Outcomes of studies that report barriers and enablers influencing uptake/maintenance of exercise in older adults with MCI/dementia will be included.

Types of studies

The searches are not limited to specific study design. Hence, all study designs using qualitative or quantitative methodologies will be included in the review. The papers will be categorized by study design using the following categories: randomized-controlled trial, quasi-controlled trial, cohort study, cross-sectional study and qualitative study.

The language of studies

Searches will be no limitation in language publications.

Publication year

Studies published between January 1990 and February 2020.

Information sources

The following electronic databases: PubMed, Embase, The Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), and the Wan Fang Database will be searched from January 1990 to February 2020 about Human studies. In order to improve the completeness of the literature, grey literature sources will be considered. We will further check the reference list of the included studies and relevant reviews.

Search strategy

Based on key terms from previous literature reviews and Medical Subject Headings, our search will use both the medical subject headings and text word and will combine concepts for the influencing factors of adherence. Our search strategy will consist of three parameters: disease (MCI/dementia), intervention (exercise) and outcome (adherence). The search strategy we will use for the retrieval of reports of trials from PubMed is summarized in Table 1. The search strategy will be modified as necessary for other databases.

Table 1 The search strategy of PubMed

Number	Search items
1	Dementia OR Cognitive Dysfunction OR Mild Cognitive Impairment* OR MCI OR VCI OR AAMI OR SMC OR ACMI OR ARCD OR CIND OR (nMCI or aMCI or mMCI or MCIa) OR MCD OR AACD OR MNCD OR Mild Neurocognitive Disorder* OR cogn* OR Cognitive impairment OR Alzheimer OR AD OR Alzheimer's disease
2	Ageing OR aging OR Elderly OR "Aged,80 and over" OR "Old* age*" OR "middle age*" OR "old* adults" OR senior* OR senior citizens OR old people OR old person

3	Exercise OR Physical activit* OR Treadmill training OR Balance OR Strength OR Endurance OR Attention training sport* OR jogging OR physical therapy OR physiotherapy OR exercise* OR fitness OR rehabilitation OR flexibility OR aerobic training OR resistance training OR motor activit* OR leisure activit* OR strength OR balance OR aerobic* OR physical* OR training OR bicycling OR cycling OR swim* OR gym* OR walk* OR danc* OR yoga OR joga OR tai chi OR tai ji OR taichi OR Taijiquan OR tai-chi OR pilates OR movement OR recovery of function OR inactivit* OR sedentary OR physical inactivit* OR occupational therapy OR physical stimulation OR physical education OR physical medicine OR resistance OR mind-body OR Mind Body OR mind body OR mind-body training
4	barrier* OR enabler* OR motivators OR facilitators OR implementation OR adherence OR compliance OR support OR self-efficacy OR self efficacy OR self-efficiency OR motivation OR experience* OR perspective* OR factor* OR attendance OR predictor*OR preference*
5	1 and 2 and 3 and 4

The selection process of studies

The study selection process will be reported according to the PRISMA flowchart.[36] First, removing duplicates using the reference manager software Endnote X7. Then titles and abstracts of articles will be screened. Selected full-text articles will be assessed for eligibility. The process will be carried by two independent researchers (HY and YX C), disagreement will be solved by discussion. A third researcher (CX G) will be invited in case of persistent contradiction. In the final, two other authors (HQ C and JW) will assess potentially eligible full-text studies to make sure if they meet the criteria set for inclusion.

Risk of bias (quality) assessment and meta-bias

Two independent reviewers rigorously will assess the quality of each paper. The Newcastle-Ottawa Scale (NOS) will be used to assess the quality of cohort articles.[37] Cross-sectional studies will be examined using the Agency for Healthcare Research and Quality (AHRQ).[38] Randomized controlled trials will be assessed according to PEDpro.[39] The

Joanna Briggs Institute (JBI) critical appraisal checklist will be used to assess the quality of quasi-randomized controlled trials.[40] Qualitative research will adopt the tool that JBI made critical appraisal tools for qualitative research in 2016.[41]

Data extraction and synthesis

Because of this expected significant heterogeneity in the included studies in terms of methods, participants, interventions and study types may limit our ability to conduct a meta-analysis. It will be the main limitation of the study. A narrative synthesis is planned as informed by the published guidelines.[42] 'Narrative synthesis' refers to an approach to the systematic review and synthesis of findings from multiple studies that rely primarily on the use of words and text to summarize and explain the findings of the synthesis.[42] Narrative methods have long been recognized as useful for investigating heterogeneity across primary studies and developing an understanding of which aspects of an intervention may be responsible for its success.[43]

Therefore, this review will adopt a narrative synthesis to synthesize all related qualitative and quantitative literature. After the full-text screening, all included studies will be imported into NVivo.12 for data extraction using a line by line approach and coding of the data. The extracted information will include study characteristics and modifiable enablers and barriers of exercise adherence in older adults with MCI/dementia. Study characteristics are as follows:

(1) Bibliographic information: the journal name, title, first author's name, publication year, language of the study, country of the corresponding author.

(2) Study design: the specific type of study, exercise intervention technique, duration, outcomes measured, instruments used to measure them, sample size and quality of the study.

(3) Participants data: type of disease, disease screening tools/diagnostic tools, setting, inclusion and exclusion criteria, sociodemographic characteristics (e.g. age, ethnicity, country).

(4) Outcomes: definition of adherence and rate of adherence. Adherence was defined as the percentage of attended sessions during the programs as registered by the instructors in most studies.[14] Generally considering that participants meet the requirement of adherence

when they complete more than seventy percent sessions of the whole program.[44-46] Yet, there is not an accepted standard for exercise adherence. Grove and Spier defined adherence as the percentage of older adults who attended ninety percent of sessions.[47] Keogh et al. described adherence as having attended one session a week over the previous 3 months.[48] It is acknowledged that there is a large difference in the definition of exercise adherence. We will describe the definition of exercise adherence in selected studies. It may be helpful for us to analyze the differences in research results and make the study more transparent.

The TDF is defined a priori framework to reflect all coding of data. Coding of data will include such as authors' descriptions of the results and all relevant quotes from participants provided in the results section (or results tables) of included studies. We will map the modifiable barriers and enablers of exercise adherence into following14 domains with 14 coding information of the TDF: (1) Knowledge, (2) Skills, (3) Social influences, (4) Memory, attention and decision processes, (5) Behavioural regulation, (6) Professional/Social role and identity, (7) Beliefs about capabilities, (8) Belief about consequences, (9) Optimism, (10) Intentions, (11) Goals, (12) Emotion, (13)Environmental context and resources and (14) Reinforcement. (15)Any barriers/enablers that do not fit within the existing domains of the TDF will be organized into the 'Others' domain.[49]

In the NVivo.12, we will build three themes from the perspective of the patients, caregivers and health care professionals to conform to the aim of our study. Each theme will be divided into two subthemes (modified barriers and enablers). For each of these subthemes, we will create 15 domains. For example, if we extracted the following text in a study 'Participant A reported that the intensity of the program was too high that affected his/her maintenance'. We would code it into TDF domain 'Goals'. Then we will compare our coding to generate consensus about identified barriers and enablers in the literature. It will be possible that the same sentence will be assigned more than one code. This process will be undertaken and will be discussed by two authors (XT Z, HQ C). Any disagreement between the two researchers will be resolved through further discussion and adjudication by a third reviewer (J W). When there is a disagreement in different study facing the same factor affecting exercise adherence, we will evaluate the state of the literature (such as literature

quality, types of research, sample size and so on) and explain potential differences in results across studies. Poor methodological quality will not be included in the review that will affect the trustworthiness of the synthesis. In the meantime, we will take some measures to minimize bias, for example, that studies judged to be of equal technical quality are given equal weight or if not providing a sound justification for not doing so.[42] We will also try our best to explore the influence of heterogeneity in this stage of the synthesis process.

DISCUSSION

Understanding modifiable barriers and enablers to exercise for older adults with MCI/dementia is a complex process that needs to be fully explored if we are to capitalise on the value exercise can offer. To date, existing research on this topic has not been synthesized. This review will synthesize and report qualitative and quantitative data about exercise adherence from the perspective of patients, caregivers and health care professionals.

This study will have several strengths and implications. First, the results will contribute to understanding common influencing factors to focus on how to modify barriers best and enhance enablers to increase the use and appeal for the exercise intervention. Second, it will facilitate effective access to care and treatment to help older adults with MCI/dementia have a broader adoption to exercise intervention. Third, it will have substantial implications for researchers, clinicians, and policymakers about how to provide better special care for older adults with MCI/dementia. We anticipate that this work will also be highly correlated to the public who want to engage with the exercise program. Last but not the least, this systematic review will be the first try that map modifiable barriers and enablers of exercise for older adults with MCI/dementia to the domains of the TDF. In theory, TDF is a comprehensive framework that synthesizes many behaviour change theories, which lower the risks of missing relevant theoretical constructs or including irrelevant ones. Hence, it can be used for summarizing the related factors of exercise adherence reported in the literature from all angles. From a practical point of view, the usefulness of TDF has been confirmed in various medical practices gradually. In view of the effectiveness of TDF, it therefore offers an appropriate framework to synthesize extensive barriers and enablers reported in single studies. The results will also provide a more in-depth insight into the influences on evidence-based

behaviour change. Findings based on the framework can be used to inform the development of effective adherence interventions to assist practitioners in choosing the most suitable evidence-based exercise programs in clinical settings accordingly.

Amendments

If we need to amend this protocol, the date of each amendment will be accompanied by a description of the change and the rationale.

Patient and public involvement

Patients and the public were not involved at this stage of the project.

Ethical issues

The systematic review is a retrospective study, using publicly available data. As no primary data collection will be undertaken and does not require a formal ethical assessment and no informed consent are needed.

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Conflict of interest

All authors declare that we have no conflicts of interest.

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Contributors

All authors contributed to the development of the study design and search strategy. XT Z and LN W designed the study and wrote the protocol. XT Z and H Y wrote the search strategy. H Y, YX C and CX G screened the literature. WJ and HQ C checked the selected article. All authors provided feedback and approved the final protocol.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a not an update

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	15
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	15
Support			
Sources	#5a	Indicate sources of financial or other support for the review	n/a not included
Sponsor	#5b	Provide name for the review funder and / or sponsor	15
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	15
Introduction			

Rationale	#6	Describe the rationale for the review in the context of what is already known	4-8
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-10
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10-11
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12-14
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and	11

		inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11-14
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12-13
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11-12
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	n/a no meta-analysis or other statistical analysis
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	n/a no meta-analysis or other statistical analysis

Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a no meta-analysis or other statistical analysis
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a no meta-analysis or other statistical analysis
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a

Notes:

- 1b: n/a not an update
- 5a: n/a not included
- 15a: n/a no meta-analysis or other statistical analysis
- 15b: n/a no meta-analysis or other statistical analysis
- 15c: n/a no meta-analysis or other statistical analysis
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Modifiable facilitators and barriers to exercise adherence in older adults with MCI/dementia using the Theoretical Domains Framework: a systematic review protocol

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Modifiable facilitators and barriers to exercise adherence in older adults with MCI/dementia using the Theoretical Domains Framework: a systematic review protocol

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Modifiable facilitators and barriers to exercise adherence in older adults

with MCI/dementia using the Theoretical Domains Framework: a systematic review protocol

ABSTRACT

Introduction Exercise has multiple benefits on maintaining or improving cognitive function for people with mild cognitive impairment (MCI)/dementia. However, many older adults with MCI/dementia are not sufficiently active to achieve these benefits. Allowing for the current studies on exercise adherence in older adults with MCI/dementia still have some deficiencies. This paper aims : (1) to identify the modifiable facilitators and barriers to exercise adherence for older adults with MCI/dementia in terms of the perspectives of patients, caregivers and health care professionals; (2) to organise the identified factors of exercise adherence base on the Theoretical Domains Framework (TDF) among included studies.

Methods and analysis A systematic computerised literature search will be performed in the following online databases: PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wan Fang Database, which published between January 1990 and June 2020. We will identify peer-reviewed publications which examined facilitators and barriers to exercise adherence. Searches will no limitation in language publications using search terms related to exercise interventions, adherence and MCI/dementia. Two independent reviewers will screen titles, abstracts and full-text articles according to the predetermined inclusion and exclusion criteria. We will use the statistical software Nvivo.12 to manage the information. Basing on the Theoretical Domains Framework (TDF), we will map identified modifiable facilitators and barriers of literature to the domains of TDF.

Ethics and dissemination This review will summarise modifiable facilitators and barriers to exercise adherence for older adults with MCI/dementia for the first time. Ethical approval is not required as no primary data are collected. We are going to disseminate our findings to the

scientific and medical community in peer-reviewed journals. The review findings will facilitate adequate and accurate access to care and treatment to help older adults with MCI/dementia have a broader adoption to exercise.

PROSPERO registration number CRD42019117725

Strengths and limitations of this study

1. To the best of our knowledge, previous work didn't systematically map and categorise modifiable facilitators and barriers to exercise adherence about older adults with MCI/dementia, referring to the Theoretical Domains Framework.

2. Our systematic review will be the first attempt to summarise the currently available evidence on the insights of patients, caregivers and health care professionals.

3. We will perform an all-round search of published and grey literature with no restrictions on language and geographical location.

4. The main limitation of the study is that no meta-analysis or other statistical analysis will be performed in this review.

BACKGROUND

Description of the MCI/dementia condition

Mild Cognitive Impairment (MCI) is the intermediate phase between normal cognitive function and dementia, characterised by a delay in cognitive decline that is larger than expected considering a person's age and education, though without marked interference in daily-life activities.[1] The published prevalence of people with MCI is approximately 10% to 20% worldwide depending on the sample and the follow-up duration of studies.[2] People with

MCI have a heightened risk of further cognitive decline and progression to dementia. After an initial diagnosis of MCI, the incidence of dementia within 1, 5, and 9.5 years was 10-15, 60.5 and 100%, respectively.[3] Dementia is characterised by progressive and severe cognitive decline, motor deficits with or without behavioural problems causing a decrease in activities of daily living (ADL).[4] As life expectancy is getting longer worldwide, the number of people affected by MCI and dementia is steadily growing.[5] According to estimates from the World Alzheimer Report, the number of people with dementia will dramatically increase in the coming decades, from 47 million in 2015 to 131.5 million by 2050.[6] These rapidly growing numbers will have a tremendous social impact, placing a high economic burden on the health care system.[6-7]

To date, there are no definite or disease-modifying therapeutic options for dementia and MCI. For the pharmacological interventions of dementia and MCI, these drugs may initially improve cognition and slow down the clinical progression of MCI/dementia. They are not capable of stopping the underlying pathological process of disease including amyloid accumulation, tau protein aggregation, synaptic loss and neuronal death.[8-9] Currently, many non-pharmacological treatments have reported benefits on cognitive function for older adults with MCI/dementia in multiple research studies.[10-11] As one of the significant recommendations for non-pharmaceutical interventions, exercise has been consistently proved to be associated with a reduced risk of developing MCI/dementia. Exercise (aerobic training, resistance training and mind-body practice, etc.) is a promising strategy for preventing or delaying cognitive decline, and its salutary effects on cognitive function have been demonstrated in animal models and a growing number of clinical studies of older adults with MCI/dementia.[12-14]

Despite these positive findings, there remain concerns that older adults with MCI/dementia are physically inactive, and their adherence to exercise is poor.[15-16] One study with older adults with MCI showed that only 25% of participants continued to apply for the exercise programs after the end of the 12-month randomised controlled trial (RCT).[16] Only 19% of the individual with dementia completed more than two-thirds possible exercise

sessions in the other one yearlong trial study, 52% of participants just finished less than one-third of possible practices and the mean adherence rate was 33.2±25.5% in the whole sessions.[15] Thus the adherence to exercise interventions was still not optimistic for older adults with MCI/dementia, and we would need to pay more attention to relevant researches of exercise adherence.

The significance of doing this review

The positive effects of all exercise interventions depend highly on exercise adherence.[17]

Lowery D et al. also concluded that it is essential to identify factors influencing the participation among older adults with dementia in the community since only 30.7% participants have achieved the prescribed frequency of the exercise in their research.[18] To increase exercise adherence levels of older adults with MCI/dementia, there is a need to understand the factors better that affect exercise adherence in such populations. Specifically, identifying the facilitators and barriers to exercise will contribute to the implementation of the exercise intervention according to the initial protocol, which will promote the rehabilitation for older adults with dementia. Some previous studies have established the factors associated with exercise participation in community-dwelling adults with dementia, including increased energy intake, resting metabolic rate, fat-free mass, gait speed, taking≥ four medications, dizziness, lower ADL function, a history of falls, delirium and so on.[19-20]

However, the current studies on exercise adherence in older adults with MCI/dementia still have the following deficiencies:

(1) The absence of research on discussing on exercise adherence in terms of different insights

The insights of patients, caregivers and health care professionals often differ regarding the facilitators and barriers to exercise adherence due to differing priorities and knowledge of the situation.[21-28] For patients, the complicacy of symptoms can make it more difficult for older adults with MCI/dementia to participate in exercise programs. Older adults with

MCI/dementia can usually express their views and preferences about what is important to them when exercising, and it is morally and ethically necessary to consider those views.[21-22] In comparison to caring for older adults with normal cognitive function, the caregivers taking care of older adults with MCI/dementia face a substantially higher burden due to changes that are typically associated with dementia.[23-24] Relatively little is known on how caregivers of older adults with MCI/dementia manage their support arrangements, which strategies they follow and which ways are perceived as helpful or obstructive in exercise.[24-25] Therefore, opinions from caregivers should be taken into account. Furthermore, previous studies also highlighted the importance of support from health care professionals to encourage older adults with MCI/dementia to take part in the exercise.[26-27] The research has shown that participants' adherence to exercise is improved when the instructions they receive are specific and understandable from health care professionals.[28] In the meantime, many health care professionals were also concerned about participants' ability to access exercise programs.[16,27] Caregivers may build bridges in following the instructions from health care professionals and monitoring exercise implementation better.[23-25] Teamwork and collaboration among patients, caregivers and health care professionals become paramount to improve the exercise adherence for older adults with MCI/dementia. Currently, the facilitators and barriers to exercise adherence among older adults with MCI/dementia in insights of different perspectives have not been studied.

(2) The lack of the utility of a theoretical framework to organise the potential facilitators and barriers to exercise adherence

Previous studies on facilitators and barriers to exercise adherence for older adults with MCI/dementia lacked the support or elaboration of behavioural theory framework. Behavioural theory can provide potential determinants and a corresponding structure for thinking logically about these determinants and their relationships.[29] Applying a behavioural theoretical framework for assessing facilitators and barriers can effectively help develop tailored informed strategies to support the effective implementation of evidence-based practices.[30] In this study, we will rely on Theoretical Domains Framework (TDF) to classify

facilitators and barriers to exercise adherence for older adults with MCI/dementia. The TDF is a comprehensive framework that synthesises several behaviour change theories. It was developed with 12 domains and 128 constructs initially, and its validity was reevaluated by Michie et al with a refined version with 14 domains and 84 constructs.[31-32] This framework offers an appropriate structure for supporting an evidence synthesis of facilitators and barriers as it will help these factors to be linked to evidence-based behaviour change techniques. This theory has been used widely and successfully to assess facilitators and barriers, and provides a theory-driven guide for the further effective interventions.[33-35] Therefore, the TDF will contribute to overall understanding the facilitators and barriers to exercise adherence for older adults with MCI/dementia.

(3)The lack of systematic research on the modifiable factors that impact exercise adherence for older adults with MCI/dementia

It is recognised that the facilitators and barriers to targeted exercise amongst older adults with MCI/dementia are multifactorial.[16-20] Furthermore, these factors are partly unmodifiable or unavoidable that is difficult for us to change (e.g. family history, sex and age). Identification of the potentially modifiable factors, which may improve or deteriorate exercise adherence is a critical approach to design interventions. This information will serve as a reminder that guides medical staff in refining target population and intervention methods theoretically, and then contributing to developing the adherence oriented exercise programs in practice. Therefore, we first attempt to identify primary research findings of modifiable facilitators and barriers that may help to design exercise strategies to improve the effectiveness of exercise interventions further.

As summarised in the above, according to a broad-based theoretical framework for behaviour change, an overall understanding of the modifiable facilitators and barriers to exercise intervention in insights of the perspectives of patients, caregivers and health care professionals is needed. Thus we aim to conduct a systematic review to collect and summarise the available evidence on modifiable facilitators and barriers to exercise

adherence for older adults with MCI/dementia. Then this study will further categorise these modifiable factors into the domains presented in the TDF. These findings will provide medical staff recommendation with the individual-tailored exercise prescriptions and contribute to developing the strategies of long-term exercise adherence for older adults with MCI/dementia.

METHODS/DESIGN

This protocol is written following the recommendation of the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P).[36] We plan to complete the systematic review with an expected completion date of March 31, 2021. This review has been registered with the international database of prospectively registered systematic reviews in health and social care (PROSPERO; registration number CRD42019117725).

Eligibility criteria

Types of participants

Eligible studies will include any type of MCI/dementia. No limitations will be placed on the severity of MCI/dementia, length of time since diagnosis. No restrictions will be placed on the severity of depression, anxiety, psychological distress or mental health-related quality of life. These individuals will be included as follows:

(1) The people aged 65 years or older.

(2) For dementia: Including studies involving people diagnosed with any type of dementia, according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-3), Fourth Edition (DSM-4), Text Revision (DSMIV-TR), Fifth Edition (DSM-5), International Classification of Diseases, Tenth Revision (ICD-10), Mini-Mental State Examination (MMSE)/Montreal Cognitive Assessment (MOCA) score available, other alternative validated diagnostic criteria or recorded in medical records.

(3) For MCI: Including studies involving people diagnosed with any type of MCI, according to the criteria in the DSM-5 criteria, Petersen's criteria, an alternative validated diagnostic criteria, MMSE/MOCA score available, or where recorded in medical records.

(4) These will be excluded: Patients who have a severe visual or auditory impairment, serious medical conditions in major organs (heart, lung or kidney), illnesses affecting mobility or are unable to accept assessments or interventions that are required in this study for any reasons.

Types of exercise intervention

This systematic review will include all studies involving any one of exercise treatment or intervention. Exercise intervention is defined as a type of physical activity that is planned, structured and repeated over a while.[37] The eligible exercise can be categorised into resistance training, aerobic exercise, combined exercise and other types of training. Also, all organisational forms of exercise intervention (individual, group, or mixed) are eligible for inclusion. Besides, supportive strategies (face to face, telephone, email) will be eligible for inclusion. There will be no limitations about the professional background of the person sustaining the exercise interventions, additionally unsustained (self-guided/self-administered) interventions will also be eligible for inclusion.

Type of setting

Studies in any setting where exercise intervention is conducted, including health care institutions, community, home or in any geographical setting globally will be considered for inclusion.

Types of outcome measures

Outcomes of studies that report facilitators and barriers influencing uptake/maintenance of exercise for older adults with MCI/dementia will be included.

Types of studies

The searches are not limited to specific study design. Hence, all study designs using

qualitative or quantitative methodologies will be included in the review. The papers will be categorised by study design using the following categories: randomised-controlled trial, quasi-controlled trial, cohort study, cross-sectional study and qualitative study.

The language of studies

Searches will be no limitation in language publications.

Publication year

Studies published between January 1990 and June 2020.

Information sources

The following electronic databases: PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), and Wan Fang Database will be searched from January 1990 to June 2020 about Human studies. In order to improve the completeness of the literature, grey literature sources will be considered. We will further check the reference list of the included studies and relevant reviews.

Search strategy

Based on key terms from previous literature reviews and Medical Subject Headings,

our search will use both the medical subject headings and text word and will combine concepts for the influencing factors of adherence. Our search strategy will consist of three parameters: disease (MCI/dementia), intervention (exercise) and outcome (adherence). The search strategy we will use for the retrieval of reports of trials from PubMed is summarised in Table 1. The search strategy will be modified as necessary for other databases.

Table 1 **The search strategy of PubMed**

Number	Search items

1	Dementia OR Cognitive Dysfunction OR Mild Cognitive Impairment* OR MCI OR VCI OR AAMI OR SMC OR ACMI OR ARCD OR CIND OR (nMCI or aMCI or mMCI or MCIa) OR MCD OR AACD OR MNCD OR Mild Neurocognitive Disorder* OR cogn* OR Cognitive impairment OR Alzheimer OR AD OR Alzheimer's disease
2	Ageing OR aging OR Elderly OR "Aged,80 and over" OR "Old* age*" OR "middle age*" OR "old* adults" OR senior* OR senior citizens OR old people OR old person
3	Exercise OR Physical activit* OR Treadmill training OR Balance OR Strength OR Endurance OR Attention training sport* OR jogging OR physical therapy OR physiotherapy OR exercise* OR fitness OR rehabilitation OR flexibility OR aerobic training OR resistance training OR motor activit* OR leisure activit* OR strength OR balance OR aerobic* OR physical* OR training OR bicycling OR cycling OR swim* OR gym* OR walk* OR danc* OR yoga OR joga OR tai chi OR tai ji OR taichi OR Taijiquan OR tai-chi OR pilates OR movement OR recovery of function OR inactivit* OR sedentary OR physical inactivit* OR occupational therapy OR physical stimulation OR physical education OR physical medicine OR resistance OR mind-body OR Mind Body OR mind body OR mind-body training
4	barrier* OR enabler* OR motivators OR facilitators OR implementation OR adherence OR compliance OR support OR self-efficacy OR self efficacy OR self-efficiency OR motivation OR experience* OR perspective* OR factor* OR attendance OR predictor* OR preference*
5	1 and 2 and 3 and 4

The selection process of studies

The study selection process will be reported according to the PRISMA flowchart.[38] First,

removing duplicates using the reference manager software Endnote X7. Then titles and abstracts of articles will be screened. Selected full-text articles will be assessed for eligibility. The process will be carried by two independent researchers (HY and YX C), disagreement will be solved by discussion. A third researcher (CX G) will be invited in case of persistent contradiction. In the final, two other researchers (HQ C and JW) will assess potentially eligible full-text studies to make sure if they meet the criteria set for inclusion.

Risk of bias (quality) assessment and meta-bias

Two independent reviewers rigorously will assess the quality of each paper. This study will use the Newcastle-Ottawa Scale (NOS)[39] for evaluating the quality of the cohort studies, use the Agency for Health care Research and Quality (AHRQ)[40] for assessing the quality of the cross-sectional studies and apply the Physiotherapy Evidence Database (PEDro)[41] scale for estimating the quality of the randomised controlled trials. The Joanna Briggs Institute (JBI) critical appraisal checklist will be used to determine the quality of quasi-randomised controlled trials.[42] Qualitative research will adopt the tool that JBI made essential tools of appraisal for qualitative research in 2016.[43]

Data extraction and synthesis

Because of this expected significant heterogeneity in the included studies in terms of methods, participants, interventions, and study types may limit our ability to conduct a meta-analysis. It will be the main limitation of the study. A narrative synthesis will be planned as informed by the published guidelines.[44] 'Narrative synthesis' refers to an approach to the systematic review and synthesis of findings from multiple studies that rely primarily on the use of words and text to summarise and explain the results of the integration.[44] Narrative methods have long been recognized as useful for investigating heterogeneity across primary studies and developing an understanding of which aspects of an intervention may be responsible for its success.[45]

Therefore, this review will adopt a narrative synthesis to synthesise all related qualitative

and quantitative studies. After the full-text screening, all included studies will be imported into NVivo.12 for data extraction using a line by line approach and coding of the data. The extracted information will consist of study characteristics and modifiable facilitators and barriers to exercise adherence in older adults with MCI/dementia. Study characteristics are as follows:

(1) Bibliographic information: the journal name, title, first author's name, publication year, language of the study, country of the corresponding author.

(2) Study design: the specific type of study, exercise intervention technique, duration, outcomes measured, instruments used to measure them, sample size and quality of the study.

(3) Participants data: type of disease, disease screening tools/diagnostic tools, setting, inclusion and exclusion criteria, sociodemographic characteristics (e.g. age, ethnicity, country).

(4) Outcomes: definition of adherence and rate of adherence. Adherence was defined as the percentage of attended sessions during the programs as registered by the instructors in most studies.[16] Generally considering that participants meet the requirement of adherence when they complete more than seventy percent sessions of the whole program.[46-48] Yet, there is not an accepted standard for exercise adherence. Grove and Spier defined adherence as the percentage of older adults who attended ninety percent of sessions.[49] Keogh et al described adherence as having attended one course a week over the previous three months.[50] It is acknowledged that there is a vast difference in the definition of exercise adherence. We will describe the meaning of exercise adherence in selected studies. It may be helpful for us to analyse the differences in research results and make the study more transparent.

The TDF is defined as a priori framework to reflect all coding of data. Coding of data will include such as authors' descriptions of the results and all relevant quotes from participants provided in the results section (or results tables) of included studies.[51] We will map the modifiable facilitators and barriers to exercise adherence as the following14 domains with 14

coding information according to the TDF: (1) Knowledge, (2) Skills, (3) Social influences, (4) Memory, attention and decision processes, (5) Behavioural regulation, (6) Professional/Social role and identity, (7) Beliefs about capabilities, (8) Belief about consequences, (9) Optimism, (10) Intentions, (11) Goals, (12) Emotion, (13)Environmental context and resources and (14) Reinforcement. (15) Any facilitator/barrier that does not match with the existing domains of the TDF will be organised into the 'Others' as the fifteenth domain.[52]

In the NVivo.12, we will build three themes in terms of the perspective of the patients, caregivers and health care professionals to conform to the aim of our study. Each theme will be divided into two subthemes (modified facilitators and barriers). For each of these subthemes, we will create 15 domains. For example, if we extract the following text in a study 'Participant A reported that the intensity of the program was too high that affected his/her maintenance'. We will code it as 'Goals' in the 14 domains of the TDF. Then we will compare our coding to generate consensus about identified facilitators and barriers in the literature. It will be possible that the same sentence will be assigned more than one code. This process will be undertaken and will be discussed by two researchers (XT Z, HQ C). Any disagreement between the two researchers will be resolved through further discussion and adjudication by a third reviewer (J W). When there is a disagreement in the different studies with the same factor affecting exercise adherence, we will evaluate the characters of the literature further, including the literature quality, types of research, sample size etc., and explain potential differences in results across studies. Poor methodological quality will not be included in the review that will affect the trustworthiness of the synthesis. Meanwhile, this study will take some measures to minimise all of the potiential biases, including providing the equal weights to the studies with the comparable technical quality, and providing a reasonable justification for not doing so.[44] We will also try our best to explore the influence of heterogeneity in this stage of the synthesis process.

DISCUSSION

Understanding modifiable facilitators and barriers to exercise adherence for older adults with MCI/dementia is a complex process that needs to be fully explored if we hope to obtain the benifits of exercise intervention in greatest extend. To date, existing research has not studied this topic. This review will synthesise and report qualitative and quantitative data about exercise adherence in terms of the perspective of patients, caregivers and health care professionals.

This study will have several strengths and implications. First, the results will contribute to understanding the common influencing factors to focus on how to modify barriers best and enhance facilitators to increase the utility and appeal for the exercise intervention. Second, it will facilitate sufficient access to care and treatment to help older adults with MCI/dementia have a broader adoption to exercise intervention. Third, it will have substantial implications for researchers, clinicians, and policymakers to provide individually tailored care for older adults with MCI/dementia. We anticipate that this study will also be highly correlated to the public who want to engage with an exercise program. Last but not least, this systematic review will be the first try that maps modifiable facilitators and barriers of exercise adherence for older adults with MCI/dementia to the domains of the TDF. In theory, TDF is a comprehensive framework that synthesises several behaviour change theories, which lower the risks of missing relevant theoretical constructs or including irrelevant ones.[31] Hence, it can be used for summarising the related factors of exercise adherence reported in the previous studies. The results will also provide a more in-depth insight into the influences on evidence-based behaviour change of exercise adherence. Findings based on the framework of the TDF can be used to inform the development of effective exercise adherence strategies and assist practitioners in selecting the most suitable evidence-based exercise programs in clinical settings accordingly.

Amendments

If we need to amend this protocol, the date of each amendment will be accompanied by a

description of the change and the rationale.

Patient and public involvement

Patients and the public are not involved at this stage of the project.

Ethical issues

The systematic review is a retrospective study using publicly available data. As no primary data collection will be undertaken and not requiring a formal ethical assessment and no informed consent are needed.

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Conflict of interest

All authors declare that we have no conflicts of interest.

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Contributors

All authors contributed to the development of the study design and search strategy. XT Z and

LN W designed the study and wrote the protocol. XT Z and H Y wrote the search strategy. H Y, YX C and CX G screened the literature. J W and HQ C checked the selected article. H T refined the English expression of this article. All authors provided feedback and approved the final protocol.

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Reporting checklist for protocol of a systematic review.

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Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a not an update

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	15
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	15
Support			
Sources	#5a	Indicate sources of financial or other support for the review	n/a not included
Sponsor	#5b	Provide name for the review funder and / or sponsor	15
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	15
Introduction			

Rationale	#6	Describe the rationale for the review in the context of what is already known	4-8
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-10
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10-11
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12-14
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and	11

		inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11-14
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12-13
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	11-12
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	n/a no meta-analysis or other statistical analysis
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	n/a no meta-analysis or other statistical analysis

Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a no meta-analysis or other statistical analysis
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a no meta-analysis or other statistical analysis
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a

Notes:

- 1b: n/a not an update
- 5a: n/a not included
- 15a: n/a no meta-analysis or other statistical analysis
- 15b: n/a no meta-analysis or other statistical analysis
- 15c: n/a no meta-analysis or other statistical analysis
- 16: n/a no meta-analysis or other statistical analysis This checklist was completed

on 12. February 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai