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The impact of late-life depression on cognitive performance in older adults with mild cognitive impairment: a systematic review protocol

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Abstract

Introduction Late-life depression (LLD) is associated with significant impairment in cognitive functions including memory, processing speed, and executive functions. Although depression is a well-established risk factor for the progression from mild cognitive impairment (MCI) to dementia, there is still no consensus in the literature regarding the specific impact of this comorbidity on the neuropsychological profile: while some studies suggest a predominantly dysexecutive profile, others emphasise deficits in attention or in memory. This divergence in findings reflects a clear knowledge gap regarding the precise cognitive signature of this comorbidity. To address this knowledge gap, this study aims to (1) determine whether older patients with MCI and depressive symptomatology exhibit poorer cognitive performance than those with MCI alone and (2) identify the specific cognitive domains most affected. The findings will inform diagnostic accuracy, prognostic evaluation, and personalised treatment strategies within this clinical population.

Methods and materials This protocol follows the PRISMA-P and PRISMA guidelines for systematic review protocols and systematic reviews. The research question and article selection criteria are defined according to the PICOS method. The search strategy will combine the main concepts, depression, mild cognitive impairment, and older adults, and will be implemented in the following databases: PubMed, Cochrane, and Web of Science. Two reviewers will independently screen the retrieved records. Risk of bias will be assessed using the JBI checklist. The following data will be synthesised: (i) the diagnostic criteria employed for MCI, (ii) the measures used to quantify depression, (iii) the specific cognitive functions assessed, (iv) the instruments utilised for cognitive evaluation, and (v) the comparative results of cognitive performance between the MCI + LLD and MCI-only groups. Finally, the GRADE system will be applied to assess the certainty of the cumulative evidence.

Discussion By integrating the available findings, this review will inform future research on the relationship between MCI and LLD and provide evidence-based guidance for clinical interventions, clarifying prognostic and treatment pathways and thereby advancing the knowledge and clinical management of these conditions.

Systematic review registration PROSPERO registration number: CRD42025607733.

Keywords Mild cognitive impairment, Neurocognitive disorder, Late-life depression, Elderly depression, Cognitive dysfunction

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Introduction

Late-life depression and its cognitive burden

Late-life depression (LLD) is described as a major depressive episode in people 60 years old or over, which may present as recurrent episodes following early-onset depression or a first episode manifesting later in life [1]. Globally, depression affects approximately 5% of the older adult population, posing a significant challenge to public health systems due to its association with increased morbidity [2]. The clinical relevance of LLD is significant, as the profile of neuropsychological impairment and the response to treatment vary according to the age at which depression occurs [3]. Specifically, individuals diagnosed with depression exhibit impaired cognitive functions, including reduced processing speed, memory, executive function, and attention [4]. These impairments are often of moderate-to-severe magnitude and serve as strong predictors of poor functional outcomes and reduced quality of life [5]. Consequently, current public health initiatives focus heavily on the prevention and control of LLD, as managing depressive symptoms early in older adults is critical to mitigating severe long-term functional and cognitive decline [2, 4].

Mild cognitive impairment and its intersection with depression

Beyond its direct neuropsychiatric burden, depression is also a key modulator of other trajectories of cognitive decline. Within the spectrum of cognitive decline, mild cognitive impairment (MCI) has been conceptualised as a stage preceding Alzheimer's disease (AD), thus informing its study and driving research towards the potential early detection of this disease [6]. Since 1989, when Reisberg et al. [7] introduced the concept of MCI, the diagnostic criteria for MCI have undergone revision by several research groups [8–14]. This evolution is also reflected in the DSM-5, which introduced the term "mild neurocognitive disorder" (mNCD) [15]. The classification of MCI/mNCD into different subtypes depends on whether deficits—with or without concomitant memory impairment—impact a single or multiple cognitive domains, often indicating underlying aetiologies such as vascular or psychiatric factors [9] suggesting that not all MCI imply an underlying AD [8]. While research indicates that patients may or may not progress to neurodegenerative disease [9, 16–21], several risk factors have been identified as increasing this likelihood, including advanced age, vascular risks, unhealthy lifestyle, and notably, depression [22–25]. In this regard, the relationship between cognitive impairment and affective disorders is complex; dynamic clinical evidence suggests that MCI itself may actively predispose or result in LLD, creating a bidirectional burden that complicates the clinical outcome [3, 5]. However, the presence of LLD in MCI patients significantly exacerbates the risk of progression to dementia [26]. Despite global initiatives such as the WHO's Global Action Plan on the Public Health Response to Dementia [27], which prioritises early detection and risk reduction, the intersection of mental health and cognitive decline remains insufficiently addressed in clinical guidelines. This gap is clinically relevant given the plausible pathophysiological mechanisms linking both conditions, including shared cerebrovascular burden, neuroinflammatory processes, and the depletion of cognitive reserve [23–26], which further underscore the importance of characterising the specific cognitive profile of this comorbidity.

Rationale and knowledge gap

Within this context of bidirectional risk, several studies have explored the influence of depression on MCI, with particular focus on its prevalence [28] and the rate of progression to AD [4, 26, 29–31]. In this sense, depression is the most reported neuropsychiatric symptom in patients with MCI ranging between 16 and 55% [32, 33], and patients with MCI and comorbid depression have a probability of up to 31% and 85% of developing neurodegenerative diseases of any type, including AD and vascular dementia [26, 29, 31]. However, a significant gap remains in the literature regarding the specific nature and severity of the cognitive impact that depression imposes on MCI. Limited research has evaluated the degree to which comorbid depression exacerbates cognitive impairment in individuals with MCI, and there is no consensus on which specific cognitive functions are most adversely affected. While some authors report a predominantly dysexecutive profile [29], others highlight impairments in attention and processing speed [4, 30]. Furthermore, it remains unanswered whether these deficits are merely additive or if they reflect a distinct synergistic pathology. A systematic review represents the most rigorous approach to reconcile these disparate findings and provide a comprehensive comparison, and to date, no systematic review has been conducted to clarify and synthesise the evidence on the differences in cognitive performance between older patients with MCI with and without depression. Consequently, the following article presents the protocol for conducting a systematic review under the following research question: do older patients with MCI and depressive symptomatology (LLD) exhibit

Table 1 Eligibility criteria

Criteria	Inclusion	Exclusion
Population	Age 60 and over Patients with the diagnosis of MCI (or mNCD) with LLD	Patients with comorbid neurological or psychiatric disease, or dementia
Methods	Depressive symptoms and cognitive performance should be measured and assessed with a validated clinical test or scale	Studies where depressive symptoms are assessed using only clinical criteria Studies that do not report the measures used for cognitive performance
Comparator	Cognitive performance between MCI and MCI with LLD	
Language	English or Spanish	
Types of studies	Observational, cross-sectional, and longitudinal studies (prospective and retrospective), provided that baseline data are available	Systematic reviews and meta-analysis. Clinical trials. Other non-peer-reviewed publications. Sources (doctoral theses, conference papers, clinical practice guidelines, government reports, educational documents)
Year of publication	All years	No restriction

The criteria summarised in this table will be applied sequentially during a two-stage screening process (title/abstract and full-text), conducted independently by two reviewers

poorer cognitive performance than patients with only MCI? Moreover, the results of the studies to be analysed will provide the foundation for a subsequent inquiry into the cognitive domains in which these patients are particularly affected.

Study objective

The primary objective of the review is to clarify the differences in cognitive performance between older patients with MCI and comorbid depression (MCI+LLD) and those with MCI alone (the comparator). Furthermore, the analysis of neuropsychological profiles may facilitate the generation of clinical hypotheses concerning the aetiology and prognosis of MCI, a process that is imperative for guiding treatment decisions and advancing research on the role of depression in MCI and progression to dementia.

Methods and materials

This protocol adheres to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [34, 35] and the systematic review will adhere to the PRISMA 2020 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [36] and was duly registered in the PROSPERO database (CRD42025607733) on 31 January 2025. In accordance with the pre-specified PICOS framework [37], the formal risk-of-bias assessment, and the based appraisal of the certainty of evidence, this protocol corresponds methodologically to a systematic review rather than a scoping review, the latter typically following the PRISMA extension for scoping reviews (PRISMA-ScR) and not requiring a formal appraisal of methodological quality or certainty of evidence.

Eligibility criteria

The inclusion and exclusion criteria for studies in the systematic review were established on the basis of the Population, Intervention, Comparison, Outcomes and Study (PICOS) method [37]: (P) Population: individuals diagnosed with LLD and MCI or mNCD; (I) Intervention: the evaluation of cognition and depression must be standardised and conducted via validated clinical instruments, with these instruments being applied to all groups; (C) Comparator: MCI vs. MCI+LLD; (O) Outcomes: influence of depression on cognition; (S) Studies: cross-sectional and longitudinal with initial comparator outcomes.

The inclusion and exclusion criteria for the studies to be selected for the systematic review are outlined in Table 1. These criteria will be applied independently by two reviewers in two consecutive screening stages, first to titles and abstracts, and subsequently to full-text records, with any disagreements being resolved by consensus or, where necessary, by consultation with a third reviewer. To guarantee the highest methodological rigour for this systematic review, search strategy across databases is restricted to peer-reviewed scientific journals. Furthermore, the multi-stage independent screening and the subsequent risk of bias assessment ensure a tight, high-quality synthesis of the current literature. Regarding the language of publication, only studies published in English or Spanish, corresponding to the language proficiency of the review team, will be considered eligible; records published in other languages will be excluded (Table 1).

Types of participants

The participants must be individuals who have been diagnosed with MCI or mNCD according to the established

criteria for such diagnoses. Studies defining MCI exclusively through screening test thresholds (e.g. MMSE or MoCA cut-off scores) will be excluded. Furthermore, at least one of the groups participating in the study in addition to meeting this diagnostic criterion for MCI must present LLD, which is defined as depressive symptomatology manifesting in individuals aged 60 years or older [1]. Studies in which the target population as verified through examination of the diagnostic criteria reported in the Methods and materials section of each study, or those suffering from other neurological or psychiatric disorders would be excluded from the review.

Types of interventions

All studies included in the review must have applied a standardised evaluation of cognitive performance and depressive symptoms via quantified and validated clinical instruments administered to all participant groups.

Types of comparators

The selected studies should provide comparative results in terms of cognitive performance between at least two groups: (1) patients with MCI + LLD and (2) patients with only MCI or a mNCD. In this regard, they must determine whether the group with cognitive impairment and late-life depression has worse cognitive performance than the group with cognitive impairment alone.

Outcome

The primary outcome will be cognitive performance, assessed either in a global manner or by specific cognitive domains, provided that it has been measured via validated neuropsychological tests or standardised scales. The quantification of depressive symptomatology should also have been conducted using a clinically validated scale.

Furthermore, data regarding the diagnostic criteria employed for MCI and depression, the instruments utilised to assess depression and cognitive functions, and sociodemographic and cultural variables (e.g. age, educational level, gender) will also be collected. These data will not be included in the inclusion or exclusion criteria, but they will be considered in the analysis and discussion of the results.

Types of studies

Observational studies, specifically those in which a group of MCI patients without depression is used as a comparator for the MCI + LLD group, will be included. Cross-sectional and longitudinal studies (prospective and retrospective) will also be selected. Longitudinal studies to be included in the review must provide information on cognitive performance at baseline and comparatively between MCI and MCI + LLD.

Systematic reviews, meta-analyses, and randomised clinical trials (RCTs) will not be included in this study. It is evident that other sources, including but not limited to doctoral theses, conference papers, clinical practice guidelines, government reports, and educational documents, are not considered either.

Studies to be included must present comparative results regarding the cognitive performance of the study groups, regardless of whether the study's ultimate objective is different.

There will be no restrictions regarding the year of publication of studies. Finally, the language will be Spanish or English.

Search strategy

The search strategy will be implemented in the following databases: PubMed, Cochrane, and Web of Science (WoS). The search equation has been constructed via high-frequency words extracted from the relevant literature as follows: depress* AND ("mild cognitive impairment*" OR "mild neurocognitive disorder*") AND (elderly OR "older adult*" OR senior* OR aging).

Data collection and analysis

Subsequent to the search in the selected databases, the Rayyan tool [38] will be employed for storage, deduplication, sorting, and data extraction. Two reviewers will independently screen the titles and abstracts of the identified records, followed by a full-text review of the selected articles according to the pre-specified inclusion and exclusion criteria. Any discrepancies between reviewers will be resolved through consensus or, if necessary, by consultation with a third independent reviewer.

Extracted data will be managed and synthesised using Microsoft Excel. The following data will be extracted: study reference, sample number, sociodemographic data (age, educational level, sex, etc.), scale for the measurement of depression, diagnostic criteria used for mild cognitive impairment, cognitive functions assessed, instruments used for the assessment of cognitive functions, and comparative results of the cognitive performance of the MCI and MCI + LLD groups.

Risk of bias assessment

The Joanna Briggs Institute (JBI) checklist [39] will be used to assess the quality of the included studies. For cross-sectional studies, the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies will be utilised. The assessment encompasses several domains, including the establishment of clear inclusion criteria,

the delineation of subjects and setting, the validation and reliability of exposure and outcome measurements, the identification and management of confounding factors, and the judicious utilisation of statistical analysis. Furthermore, the JBI Critical Appraisal Checklist for Cohort Studies is a tool designed to evaluate longitudinal studies, encompassing both prospective and retrospective designs, in which participants are observed over time to ascertain cause–effect relationships. The following aspects are assessed: comparability between exposed and unexposed groups, adequacy of exposure and outcome measures, identification and control of confounders, and adequate and complete follow-up of participants.

Consequently, the Checklist for Analytical Cross-Sectional Studies will be employed for cross-sectional studies, and the Checklist for Cohort Studies will be utilised for longitudinal studies.

Synthesis of results

The synthesis of the results will be based on data extraction following a qualitative synthesis without meta-analysis methodology (SWiM) [40] described above. The maximum importance is given to the objective of the study. The cognitive performance of individuals with MCI vs. MCI with LLD, as well as the instruments used for cognitive assessment, will be detailed and synthesised. As this protocol is designed for a narrative, non-meta-analytic synthesis, the predefinition of quantitative subgroup analyses is not appropriate. Nevertheless, where the available data permit, an additional narrative exploration will be conducted according to relevant study characteristics, such as the MCI subtype, the diagnostic method used for depression, the specific cognitive domains assessed, and, where reported, sociodemographic and contextual variables including age, sex, education, and study setting (e.g. community-dwelling versus clinical samples), in order to provide a more nuanced interpretation of the findings.

Assessment of the certainty of evidence (confidence in cumulative evidence)

To address the PRISMA guidelines [36], the GRADE (Grading of Recommendations Assessment, Development and Evaluation) [41] system will be implemented to assess the certainty or strength of the cumulative evidence supporting the conclusions of the systematic review.

Despite the use of qualitative synthesis (SWiM) [40], the GRADE [41] approach will be adapted to provide a structured and transparent judgement on the reliability of the findings for each cognitive outcome analysed. The certainty of the evidence will initially be classified as high and will be downgraded based on the following domains, integrating information already planned in this protocol:

1. Risk of bias: Certainty will be downgraded if a significant proportion of included studies show a high risk of bias, as determined by the JBI Critical Appraisal Checklists [39].
2. Inconsistency (heterogeneity): Heterogeneity (clinical or statistical), which is recognised as a protocol limitation, will be assessed. If study results notably differ in the direction or magnitude of depression's effect on a specific cognitive domain, the certainty of the cumulative evidence will be downgraded.
3. Indirectness: The alignment of the population, interventions (assessment), and outcomes of the studies with the PICOS criteria [37] will be considered. The presence of indirect evidence results in certainty being downgraded.
4. Imprecision: Certainty will be downgraded if conclusions are based on a limited number of studies or if the samples reported in the primary studies are consistently very small.
5. Publication bias: Although no formal statistical tests for this bias are specified, the risk of publication bias, identified as a limitation of the protocol, will be factored into the final judgement of evidence certainty.

Patient involvement

None. Patient participation is not a prerequisite for conducting a systematic review.

Expected results

The findings of this systematic review will be presented through descriptive tables and qualitative synthesis following the SWiM guidelines. Specifically, the results will clarify the exact cognitive domains that may be significantly altered by the coexistence of LLD in patients with MCI. By accurately mapping these outcomes, the review aims to provide a definitive overview of whether depression induces a distinct neuropsychological phenotype or acts as an additive factor in cognitive decline, ensuring a clear and comprehensive dissemination of the synthesised data. In addition, and where the available data permit, the results will explore potential differences in the cognitive impact of this comorbidity according to age, sex, education, and study context, thereby identifying subgroups that may be particularly vulnerable to the cognitive consequences of comorbid LLD and MCI. From a clinical standpoint, these findings are expected to support earlier and more precise identification of high-risk neuropsychological profiles among older adults with MCI and comorbid depression, thereby informing individualised assessment and intervention strategies. From a scientific standpoint, they will help delineate priority

areas for future hypothesis-driven research into the mechanisms underlying the LLD–MCI relationship.

Discussion

This protocol establishes a rigorous methodological framework for systematically mapping and synthesising the impact of comorbid depression on the cognitive profile of older adults with mild cognitive impairment (MCI). Although the association between depression in older adults (LLD) and cognitive impairment is well documented, their coexistence often complicates differential diagnosis and prognostic accuracy. By generating a clearer picture of the cognitive profile associated with this comorbidity, this review is also expected to contribute to international public health priorities such as the WHO Global Action Plan on the Public Health Response to Dementia [27], which explicitly calls for a closer integration of mental health and cognitive decline within clinical guidelines.

The main strength of this review lies in its potential to determine specific cognitive profiles. By comparing patients with MCI alone to cohorts with MCI + LLD, we aim to clarify whether depression acts as a simple additive factor or whether it creates a distinct neuropsychological phenotype. This distinction is crucial; for example, identifying a predominant executive deficit in patients with MCI + LLD could support the hypothesis of "vascular depression" or suggest a specific vulnerability in prefrontal-subcortical circuits. Conversely, synergistic memory worsening could point to an increased risk of rapid conversion to AD, as depression is often considered a prodromal manifestation of neurodegeneration.

In contrast to previous narrative reviews, this protocol utilises a rigorous PICOS framework [37], deliberately excluding studies based solely on screening tests (e.g. MMSE thresholds). By requiring validated clinical criteria for both MCI and LLD, we ensure that the synthesised evidence reflects real clinical entities rather than transient cognitive fluctuations. Furthermore, the integration of the SWiM (synthesis without meta-analysis) [40] approach and the GRADE [41] system provides a transparent and structured judgement on the certainty of the evidence, a step that is often omitted in qualitative systematic reviews. This ensures that our conclusions can be directly translated into clinical guidelines with a known level of confidence.

Beyond these phenotypic considerations, the cognitive profile emerging from the synthesis may also help to clarify the underlying pathophysiological mechanism linking LLD and MCI, including cerebrovascular burden, neuroinflammation, and the depletion of cognitive reserve [23–26, 42]. In this regard, the planned narrative exploration by age, sex, education, and study context may further help to identify subgroups of older adults who are particularly vulnerable to this comorbidity, informing more targeted screening and management approaches.

Anticipated challenges and limitations

We anticipate significant heterogeneity in the way cognitive domains are assessed in the literature. The variety of neuropsychological batteries and different diagnostic thresholds for MCI (e.g. DSM-5 versus GDS scores) may pose challenges for synthesis. However, by classifying the results into specific domains (attention, executive function, memory, processing speed), this review will provide a much-needed "map" of where the strongest evidence lies and where more primary research is required.

Future implications

Ultimately, the results generated by this systematic review will serve a dual purpose. For clinicians, it will provide a more precise framework for the neuropsychological assessment of older adults, facilitating personalised intervention strategies (e.g. prioritising cognitive stimulation or pharmacological treatment of mood). For the scientific community, it will highlight gaps in the current understanding of the interface between MCI and depression, particularly regarding the role of educational attainment and other sociodemographic moderators.

Abbreviations

LLD	Late-life depression
MCI	Mild cognitive impairment
AD	Alzheimer's disease
mNCD	Mild neurocognitive disorder
PRISMA-P	Preferred reporting items for systematic review and meta-analysis protocols
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
JBI	Joanna Briggs Institute
SWiM	Synthesis without meta-analysis methodology
GRADE	Grading of Recommendations Assessment, Development and Evaluation

Supplementary Information

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Supplementary Material 1.

Statement

This manuscript was translated with the assistance of AI-based tools. The authors reviewed and edited the content to ensure accuracy and clarity.

Authors' contributions

All the authors (OPS, BPA, JAI-A, and AGC) participated in the preparation of this protocol, provided feedback, and discussed and approved the manuscript's final submission.

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Data availability
The datasets used and/or analysed during the current study will be available from the first author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethics committee approval was not a prerequisite for this protocol and systematic review, as the publication of research results will be undertaken without access to primary or confidential patient data. The results of the systematic review will be presented in scientific journals, congresses, and dissemination channels of Universidad Loyola Andalucía.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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