

Association between perceived psychological stress and cognitive decline in aging: a systematic review protocol

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Review question/objective: The objective of this review is to identify, appraise and synthesize the best available evidence on the association between perceived psychological stress and cognitive decline in aging.

Keywords Aging; cognitive decline; perceived psychological stress

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Background

Cognitive disorders such as Alzheimer's disease and other types of dementia are considered the most devastating illnesses worldwide, affecting over 36 million individuals.¹ Dementia is estimated to double by 2030 and more than triple by 2050, with the highest rates occurring in middle- and low-income countries.¹ The World Health Organization has recently established dementia as a public health priority in the global health agenda, highlighting primary prevention measures as the main target of strategies to delay disease onset, even to a modest degree, and to modify dementia prevalence worldwide.² Identification of preclinical stages and modifiable risk factors for dementia constitutes the central focus of prevention measures.² Subjective cognitive impairment (SCI) and mild cognitive impairment (MCI) have attracted special attention from the scientific community, given their association with the high risk of dementia.^{3,4} Subjective cognitive impairment is described as a persistent complaint of poor performance in memory or other cognitive domains such as attention or executive function; in SCI, however, no abnormalities are detected on neuropsychological assessment.³ This differs from MCI, which requires evidence of cognitive deterioration based on objectively measured decline, with preserved independence in functional

abilities and complex instrumental activities of daily living.⁴ Given that neurodegeneration may precede the onset of dementia by several years, individuals with SCI and MCI represent target populations so as to better identify preclinical signs and modifiable risk factors and to support primary preventive strategies.^{3,4} Indeed, interventions to minimize exposure to these risk factors, such as improvement in health services and health promotion, have demonstrated their effectiveness in reducing dementia prevalence.²

Poor cardiovascular health, low education and physical inactivity are known risk factors linked to dementia.² However, other modifiable risk factors should be identified to better detect vulnerable populations and define target interventions.² Exposure to psychological stress over one's lifespan has been proposed as a potential risk factor for dementia largely owing to the clear relationship between the biological mechanism of stress response and brain structures involved in cognitive function.^{5,6}

The concept of stress and its relationship with cognitive performance

Stress is the body's response to events that represent a real threat (i.e. natural disasters) or a relative or psychological threat induced by the interpretation of a situation as being novel, unpredictable, uncontrollable or social-evaluative.⁷ The individual's interpretation of the situation moderates the intensity of the stress reaction, which may be mild or intense.⁷ Consequently, psychological threats elicit a stress response only in certain individuals, according to their cognitive evaluation of the situation.⁷ In summary,

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psychological stress occurs when an individual perceives that a certain situation exceeds his or her coping resources whereby this cognitive interpretation triggers the stress response.⁷

When a situation is perceived as stressful, the sympathetic-adrenal medullary system is activated leading to catecholamine release. In addition, the hypothalamic-adrenal-pituitary axis ultimately triggers glucocorticoid secretion (cortisol in humans). The glucocorticoids are capable of crossing the blood-brain barrier, binding specific receptors of neurons located in the pre-frontal cortex and hippocampus, regions of the brain known to be involved in learning and memory.^{6,7} While acute stress is necessary in order to cope with adverse or challenging situations, repeated and prolonged exposure to high levels of glucocorticoids are neurotoxic and may therefore compromise cognitive performance.^{6,7}

Several authors have argued that the negative effects of stress are cumulative over the course of life, and there are windows of vulnerability throughout the lifespan whereby cortisol may be prejudicial to brain functioning; aging is one of the most vulnerable periods⁸⁻¹⁰ mainly because it reflects, in a broader sense, a period when individuals begin to perceive more substantial physical decline. The onset of this decline can occur earlier or later depending on the individual, but typically begins at around 50 years of age.¹¹ During aging, a decline in functional reserve compromises the brain's ability to compensate for insults.⁸ Prolonged exposure to stress hormones has been associated with poor memory and attentional performance among older adults and also with SCI, MCI and dementia.⁸⁻¹⁰ Although cortisol measurement has proven feasible and reliable in several biological specimens such as saliva, blood, urine and hair, this process can pose a challenge because it requires financial and laboratory resources.¹² Moreover, cortisol concentrations may be influenced by sex, sampling methods (including sample collection time), dietary habits and lifestyle. These factors must be carefully controlled.¹³

Besides biological measures of the stress response, individual perceptions of psychological stress – perceived psychological stress – is also a reliable and essential measure for understanding the negative effects of stress. Individual responses to events that are indicative of overload, such as perceived stress or event-elicited negative feelings of emotional suffering and burden, constitute one of several indicators

of perceived psychological stress. Psychometric instruments for assessing perceived stress are available with reliable psychometric properties demonstrated in several populations.¹⁴⁻¹⁶ The majority of these instruments are easy to administer, and can be self-administered and used in different settings including clinical, representing a potential option for evaluating stress.¹⁴

Similar to biological markers of stress, population-based cohort studies have also shown that adults and older individuals who perceive themselves as highly stressed have a higher risk of developing cognitive impairment than those with perceived low stress.^{17,18} Accordingly, SCI and MCI are also linked to high levels of perceived psychological stress.^{19,20}

Taken together, these findings support the hypothesis that psychological stress is associated with cognitive function. However, no systematic reviews have been conducted to determine whether psychological stress predicts cognitive decline. A search of MEDLINE, the Cochrane Library and *JBIG Database of Systematic Reviews and Implementation Reports* yielded no review protocols or reports addressing whether perceived psychological stress can predict cognitive decline in aging.

Identifying perceived psychological stress as a predictor of cognitive decline during aging can help identify modifiable risk factors for cognitive disorders and preclinical signs, elucidate factors that negatively impact on successful aging and promote the development of non-pharmacological strategies for coping with the burden of stress throughout the lifespan.

Inclusion criteria

Types of participants

The current review shall encompass studies that include male and female participants, aged 50 years or older, drawn from the community or long-term care facilities and without medical diagnosis of any type of dementia. There is no consensus on the age at which a person is defined as old.¹¹ Currently, two milestones have been considered to categorize individuals as “elderly”: one establishing “60 or 65 years and over” as a chronological point that marks late stages of life and adopted in most high-income countries; and another based on social milestones such as retirement age or transition in livelihood, typically at 50 years in most low-to-middle-income

countries.¹¹ Samples comprising older adults classified as any of the following will be included: cognitively healthy older adults (without cognitive impairment as confirmed by valid and reliable neuropsychological tests that measure cognitive domains [i.e. memory, attention, executive function and category fluency] or without a medical diagnosis of cognitive impairment), older adults with SCI (as measured by formal questionnaires or closed questions on participant's complaint of cognitive performance) and older adults with MCI, according to the National Institute on Aging-Alzheimer's Association recommendation.⁴ Given that none of these conditions fulfill criteria for a dementia condition, any of the three conditions will be considered in the studies to analyze whether psychological stress is associated with cognition. Studies involving participants with a diagnosis of dementia will not be considered, given that patients' perceptions of psychological stress may be altered due to cognitive impairment.²¹

Exposure of interest

The current review will include studies evaluating perceived psychological stress. Specifically, studies that evaluate individual perceptions about level of stress in the last 30 days (minimum) will be included. This timeframe will be considered to ascertain that the perceived psychological stress measured is related to chronic stress rather than acute stress situations. This is important to assure that the stress level perceived by the participant represents prolonged as opposed to acute exposure to stressful situations. Reliable instruments, such as the Perceived Stress Scale,²² with validated psychometric properties must have been used to assess the level of perceived stress. Other valid and reliable neuropsychological tests that measure cognitive domains will also be considered for this review.

Outcomes

The current review will encompass studies that include the following outcomes: cognitive, memory, attention or executive function declines, as well as conversion to SCI, MCI or dementia. Cognitive performance, including memory, attention and executive function, need to have been evaluated using neuropsychological tools, such as the Mattis Dementia Scale²³ or the Montreal Cognitive Assessment.²⁴

Other valid and reliable neuropsychological tests that measure cognitive domains will also be considered for this review. A decline in cognition will be defined when cognitive performance lies outside the recommended cutoff scores of the neuropsychological tools or when a poorer performance is detected compared to baseline.

Types of studies

The review will consider observational studies. These include the following designs: cross-sectional, case-control and cohort studies. Randomized controlled trials may also be included if reporting the risk of developing cognitive decline is associated with an intervention related to stress exposure.

Search strategy

The aim of the search strategy is to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE, CINAHL and PsycINFO will be undertaken, followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be performed across all databases included. Third, the reference lists of all identified reports and articles will be searched for additional studies. Studies published in English, Spanish and Portuguese with no time limit regarding the publication date will be considered for inclusion in this review.

The databases to be searched include MEDLINE, PsycINFO, CINAHL, Scopus, Lilacs, Cochrane Central Register of Control Trials and the Web of Science.

The Lilacs database will be searched for English and non-English (Spanish and Portuguese) studies.

The search for unpublished studies will include ProQuest Dissertation & Theses and Google Scholar.

Initial keywords to be used will be:

- cognitive decline
- memory
- attention
- executive function
- psychological stress
- aging
- subjective cognitive impairment
- mild cognitive impairment

- dementia
- Alzheimer's disease.

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MASARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion or via a third reviewer.

Data extraction

Quantitative data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MASARI (Appendix II). The data extracted will include specific details about the populations (study setting, sample size, socio-demographic and cognitive characteristics), study methods (study design, neuropsychological tools and psychological stress scales applied) and outcomes pertinent to the review question and specific objectives (cognitive performance assessed using neuropsychological tools and cognitive status of “cognitively normal”, “cognitively normal but with SCI”, with “MCI” or with dementia of any type). Authors of primary studies will be contacted for missing information or to clarify unclear data.

Data synthesis

Quantitative data will, where possible, be pooled in statistical meta-analyses using JBI-SUMARI. All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data), and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard Chi-square test and also explored using subgroup analyses based on the different study designs included in this review. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate. Stress level will be analyzed using both the mean scores of the instruments (stress level as continuous variable) or quantiles of stress scores (stress level as categorical variable).

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Appendix I: Appraisal instruments

MAStARI appraisal instrument

JBIC Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer Date

Author Year Record Number

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions?	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer Date

Author Year Record Number

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	☐	☐	☐	☐
2. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
3. Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
4. Were outcomes assessed using objective criteria?	☐	☐	☐	☐
5. If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer Date

Author Year Record Number

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2. Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3. Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4. Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5. Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix II: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer Date

Author Year

Journal Record Number

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting

Population

Sample size

Group A _____ Group B _____

Interventions

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:

Study results**Dichotomous data**

Outcome	Intervention () number / total number	Intervention () number / total number

Continuous data

Outcome	Intervention () number / total number	Intervention () number / total number