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Cardiovascular Comorbidities in Alzheimer's Disease: A Systematic Review and Meta-analysis

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We use this protocol and it's working. Systematic Review Protocol Cardiovascular Comorbidities in Alzheimer's Disease: A Systematic Review and Meta-analysis Juliano Flávio Rubatino Rodrigues1-3* , Lívia Peregrino Rodrigues4 , Moacir Fernandes de Godoy1 , Gerardo Maria de Araújo Filho1 1- Faculdade de Medicina de São José do Rio Preto (FAMERP), São José do Rio Preto, São Paulo, Brazil; 2- Faculdade de Medicina de Marília (FAMEMA), Marília, São Paulo, Brazil; 3- Unimed Bauru, Bauru, São Paulo, Br

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Abstract

Method

We used the PRISMA statement and defined the PECOS strategy, such as Population (P) = individuals; exposure (E) = cardiovascular disease; comparison (C) = without cardiovascular disease; outcome (O) = Alzheimer's disease; and study design(S) = all kinds of studies with an association cardiovascular disease and Alzheimer disease without time limits.

Protocol

1 Systematic Review Protocol

1.1 Introduction: Alzheimer's disease (AD) is widely recognized as the most prevalent form of dementia, affecting millions of people across the globe (Kumar et al., 2025). This progressive neurological disorder is not merely a single condition; it is intertwined with a multitude of risk factors that can heighten an individual's susceptibility. Key among these are genetic factors that predispose certain individuals to the disease, alongside a range of mental health disorders that can complicate the clinical picture (A Armstrong, 2019). Cardiovascular disease (CD) plays a pivotal role in the overall health outcomes of individuals suffering from dementia, emerging as a leading cause of mortality within this population. The intricate connections between cardiovascular health and neurodegenerative disorders, particularly vascular dementia, warrant a closer examination. Recent studies have unveiled intriguing relationships between vascular dementia and AD, indicating that these two conditions may share common underlying mechanisms. This suggests that factors influencing cardiovascular function could also affect the progression and clinical manifestations of both types of dementia, highlighting the importance of addressing cardiovascular health in the management of these neurodegenerative diseases (Kim et al., 2025). Given the complexity of the relationship between CD and AD, our aim is to undertake a comprehensive exploration of the intricate interactions that exist between these two significant health concerns. By delving into the ways in which cardiovascular health influences cognitive function and the progression of AD, we aspire to reveal valuable insights that could deepen our understanding of brain health. This knowledge could ultimately lead to the development of more effective treatment strategies and preventive measures, enhancing the quality of life for those affected by these intertwined conditions.

2 Objectives: This study aims to search for CD comorbidities with AD. Specifically, the objectives are:

2.1 To systematically review and synthesize the evidence on the association between CD and AD.

2.2 To identify common factors associated with CD and AD

2.3 To conduct meta-analyses, where feasible, to quantify the overall effect sizes of the associations between CD and AD.

2.4 To explore potential shared mechanisms and pathways through which CD and AD

3 Methods: Study design This study proposes to investigate CD associated with AD. This systematic review follows the PRISMA methodology (Page et al., 2021) with two parallel reviews. After review, a meta-analysis will proceed.

3.1 Selection criteria We used the PRISMA statement and defined the PECOS strategy, such as Population (P) = individuals; exposure (E) = cardiovascular disease; comparison (C) = without cardiovascular disease; outcome (O) = Alzheimer's disease; and study design(S) = all kinds of studies with an association cardiovascular disease and Alzheimer disease without time limits. To be eligible, studies had to meet the following criteria: They had to include a paper that reported cardiovascular disease in individuals with Alzheimer's. We excluded every study that did not describe a possible association between cardiovascular disease and Alzheimer's. Three authors systematically searched, read titles and abstracts, and shared the findings of the eligible papers. Some cardiovascular risk factors, such as diabetes and dyslipidemia, were not included as cardiovascular disease. Studies that did not distinguish Alzheimer's disease from other dementias, other vascular diseases not related to heart disease, and simple comments were excluded.

3.2 Search Strategy Following the PRISMA, the defined papers' titles and abstracts are eligible and non-restricted languages without time limits. Furthermore, it was systematically identified by searching electronic databases Embase [Emtree - Major Focus Exp.], Pubmed [Mesh Terms], and Lilacs - Complete collection of the Virtual Health Library [Title/abstracts], in November 2024.

3.3 Quality assessment It will use the Newcastle–Ottawa Quality Assessment Scale (NOQAS) to measure the methodological quality of studies, controlling for publication bias in case-control and cohort studies (2). Two reviewers (LPR and JFRR) will independently assess the studies' quality. Disagreements will be resolved through discussion and consensus or with arbitration by a third reviewer (LLC). Based on the total NOQAS score, studies will be categorized into risk of bias levels: Minimal risk of bias: Score of 7 or more; Low risk of bias: Score of 5 to 6; Medium risk of bias: Score of 3 to 4; High risk of bias: Score of 0 to 2. It will use the Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) to measure the methodological quality of studies and control for publication bias in systematic reviews (3). Quality assessment will be used to contextualize the findings. It may inform sensitivity analyses, such as excluding studies with a high risk of bias to assess the robustness of the overall results.

3.4 Data extraction The data will be extracted into two tables describing insomnia-related factors. Factors associated with insomnia in the two parallel reviews will be compared through exploratory factor analysis to identify and extract commonalities. Data extraction will be performed independently by two reviewers (JFRR and LPR) using a pre-piloted, standardized data extraction form. Discrepancies will be resolved through

discussion and consensus or with arbitration by a third reviewer (GMAF). The data extraction form will capture the following information from each included study:

3.5 Study characteristics: Author(s), year of publication, country of study, study design, sample size, population characteristics (age, gender, clinical characteristics).

3.6 Cardiovascular disease: describe how the type of CD was associated with AD.

3.7 Alzheimer's Disease characteristics: Definition and measurement of suicidal behavior/Alzheimer's disease, prevalence of outcome, assessment methods.

3.8 Association measures: Reported measures of association between Cardiovascular disease/Alzheimer's disease (e.g., odds ratios, hazard ratios, correlation coefficients), effect sizes, confidence intervals, p-values.

4 Associated factors: Variables adjusted for in analyses or examined as moderators (e.g., depression, anxiety, cognitive function, demographic factors, biological factors).

5 Key findings and conclusions of the study.

6 Data Synthesis and Meta-analysis: Meta-analyses will be conducted using SPSS software version 29 [or equivalent]. We will use random-effects models to account for potential heterogeneity between studies. Heterogeneity will be assessed using the I2 statistic, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. If substantial heterogeneity is detected (I2 > 50%), we will explore potential sources of heterogeneity through subgroup analyses (e.g., by study design, population characteristics, insomnia measurement method) and sensitivity analyses (e.g., excluding studies with high risk of bias). Publication bias will be assessed using funnel plots and Egger's test if a sufficient number of studies are included in meta-analyses (at least

6.1 2. Optional analysis:

6.2 2.1. Umbrella Review: If the systematic review demonstrates a large number of previous reviews, a joint analysis of the data can be performed.

7 Dissemination The findings of this systematic review will be disseminated through: · Publication in a peer-reviewed, internationally recognized journal indexed in PUBMED. We will target journals with a focus on sleep, psychiatry, neurology, or public health. · Preprint server deposition. We will consider posting a preprint of the manuscript on a

recognized preprint server (e.g., medRxiv, bioRxiv) to facilitate rapid dissemination of findings. · Conference presentations. We will present the findings at relevant national and international conferences. · Lay summaries. We will prepare lay summaries of the findings for dissemination to patient advocacy groups and the general public.

Project timeline

8 This systematic began on November 24 and will finish on May 25.

References

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