Mar 13, 2025

Tau and depression: A systematic review and Meta-analysis

DOI
https://dx.doi.org/10.17504/protocols.io.q26g7mqw8gwz/v1

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OPEN ACCESS

DOI: https://dx.doi.org/10.17504/protocols.io.q26g7mqw8gwz/v1

Protocol Citation: Juliano Flávio Rubatino Rodrigues 2025. Tau and depression: A systematic review and Meta-analysis. **protocols.io** https://dx.doi.org/10.17504/protocols.io.q26g7mqw8gwz/v1

Protocol status: Working
We use this protocol and it's working

Created: March 10, 2025

Last Modified: March 13, 2025

Protocol Integer ID: 124155

Keywords: tau protein in individual, tau protein levels with individual, association between tau protein, tau protein level, tau protein, describing tau protein, hyperphosphorylation of the tau protein, participants with elevated tau, elevated tau, tau value, tau, statistical difference in tau value, alzheimer disease, substantial impact on depressive illness, depressive illness, alzheimer, depression, people with depression, neurodegenerative disease, many neurodegenerative disease, such as frontotemporal dementia, phosphorylation, hyperphosphorylation, dementia

Abstract

Objectives: The tau protein is essential for stabilizing microtubules. Changes in its phosphorylation are identified in many neurodegenerative diseases, such as frontotemporal dementia and Alzheimer's disease. The hyperphosphorylation of the tau protein is linked to various factors, including stress, which has a substantial impact on depressive illness. The present study aimed to systematically review studies that describe the association between tau protein and depression.
Design: The present study used the PRISMA statement 2020 as the inclusion criterion for articles describing tau protein in individuals with depression. The exclusion criterion was the lack of comparison of tau protein levels with individuals without depression.
Results: A total of 138 papers were identified, of which 21 were ultimately included. Associations have been found between tau protein and depression. In one study, participants with elevated tau had 1.42 times more chance of being depressed. Meta analyses demonstrated no statistical difference in tau values in people with depression compared to controls.
Conclusions: The association between tau protein and depression seems uncertain. More studies with adequate sampling are necessary to improve understanding of this vital question.

Protocol to systematic reviey

1 This systematic review followed this protocol.

Protocol

2 1. Introduction:
The tau protein is essential for stabilizing microtubules, which transport nutrients in neurons. Negative phosphorylation regulates tau's interaction with microtubules. Mutations in the MAPT gene can impair this process, leading to neurofibrillary aggregates (1). Hyperphosphorylation of tau protein has been linked to numerous diseases such as diabetes, Parkinson's disease, Huntington's disease, Pick's disease, etc (2). Alzheimer's disease is the best-documented disease in which tau protein plays a pathophysiological role (3). The neuronal damage caused by the tau protein starts with its hyperphosphorylation. Several factors contribute to an imbalance between the elements that promote tau hyperphosphorylation and those that facilitate its dephosphorylation. Most hyperphosphorylation promoters hyperactivate glycogen synthase kinase-3b (GSK-3b) and inhibit PP2A phosphatase, promoting an imbalance between phosphorylation mechanisms (4). Hyperphosphorylated tau protein accumulates in neurofilaments and destabilizes microtubules with consequent neuronal atrophy and death. GSK-3b may serve as a critical junction connecting the mechanisms of tau hyperphosphorylation and the onset of depression. By delving into the physiopathology of stress, we can gain valuable insights that could enhance preventive measures against neurodegenerative diseases in older adults.

3 2. Objective:
This review aims to provide a comprehensive exploration of the current literature, focusing specifically on
the connection between alterations in tau protein levels and the experience of depressive symptoms. By systematically identifying and analyzing relevant studies, we seek to illuminate the complex interplay between tau protein dynamics and mood disorders, highlighting the implications for understanding how these biological changes may contribute to the onset and progression of depression.

4 3. Methods:
3.1. Study design
This study proposes to investigate the tau
protein associated with depression. This systematic review follows the PRISMA methodology (5) with two parallel reviews.
After review, a meta-analysis will proceed.

3.2. Selection criteria

The question (PECOS) under study was: Do individuals (P) exposed to high levels of Tau protein (E), compared to individuals with normal levels of Tau protein (C), exhibit a higher prevalence of depression (O)? Case-control studies and other kinds of study that discriminate between the control group and case of depression(S) were selected, with the inclusion criterion for articles describing tau protein in individuals with depression and the exclusion criterion being the lack of comparison of tau protein levels with individuals without depression.

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.

3.3. 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 April 2024.

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).

3.6. Analysis

One hundred and thirty-eight articles were found, eighteen of which were repeated. One was written in Spanish, one in German, four in Mandarin, and the others in English. All were read in full by one of the authors, and two read all

abstracts. The two co-authors
who read all the abstracts agreed to exclude 42 articles that did not meet the inclusion criteria and to read the four articles written in Chinese with the help of AI Chat. The author, who read all the articles in full, agreed with excluding 42 articles and noted the inappropriateness of another 57, including 21 for data extraction.
Statistical analyses were performed using SPSS version 29.

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Dissemination
The findings of this systematic review will be disseminated through:
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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.
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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.
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Conference presentations. We will present the findings at relevant national and international conferences.
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Lay summaries. We will prepare lay summaries of the findings for dissemination to patient advocacy groups and the general public.

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