

Plasma Serotonin Levels and Depression Scores in Informal Caregivers of Patients with Dementia and without Dementia: A Systematic Review

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ABSTRACT

Background: Depression frequently affects informal caregivers, particularly those caring for dementia patients due to greater emotional and caregiving burdens. This study aims to compare depression levels and plasma serotonin concentrations between dementia and non-dementia caregivers.

Subjects and Method: A systematic review was conducted using PRISMA guidelines. Articles were searched from PubMed, ScienceDirect, and Google Scholar between 2015–2024 using the keywords: dementia caregiver, non-dementia caregiver, depression, and serotonin. Nine primary observational studies met the inclusion criteria: full-text availability, adult informal caregivers, and quantitative measurement of depression and/or serotonin. Data were synthesized narratively.

Results: Most studies demonstrated higher depression levels among dementia caregivers compared to non-dementia caregivers. Emotional distress, patient behavioral symptoms, and caregiving duration were identified as major contributing factors. One study showed lower plasma serotonin associated with higher depressive scores, supporting possible biological involvement.

Conclusion: Dementia caregivers exhibit greater depressive symptoms than non-dementia caregivers, potentially linked to caregiving burden and serotonin imbalance. Early psychological screening and targeted support interventions are recommended.

Keywords: Dementia caregivers; depression; serotonin; non-dementia; mental health.

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BACKGROUND

Dementia is a progressive neurocognitive disorder characterized by significant decline in one or more cognitive domains, including complex attention, executive function, language, memory, perceptual motor ability, and social cognition. These deficits represent a decline from previous levels of functioning, occur outside the context of delirium, and interfere with independence in

everyday activities. Dementia is commonly categorized into several major subtypes: Alzheimer's disease, vascular dementia, frontotemporal dementia, Lewy body dementia, and mixed dementia—each associated with progressive functional deterioration (Arvanitakis et al., 2019).

As cognitive and functional impairments advance, individuals with dementia increasingly rely on informal caregivers for

both instrumental and basic activities of daily living. In gerontological and healthcare literature, informal caregivers are defined as individuals who provide unpaid assistance to persons with chronic illness, functional limitations, or age-related decline (Fields et al., 2020). Their responsibilities encompass physical care, medication adherence, financial management, transportation, and household tasks, as well as providing emotional and psychological support (Schulz et al., 2008). In dementia specifically, caregiving demands increase substantially as patients lose the ability to communicate, regulate behavior, and make autonomous decisions.

These intensifying demands make dementia caregiving uniquely burdensome and contribute to disproportionately high levels of psychological distress. A growing body of evidence indicates that caregivers of dementia patients consistently report greater stress and depressive symptoms compared to caregivers of individuals without dementia or those caring for patients with physical illnesses alone (Huang, 2022). This heightened burden reflects not only the physical aspects of caregiving but also enduring emotional strain caused by behavioral disturbances, personality changes, disorientation, and the progressive loss of the patient's identity a phenomenon conceptualized as ambiguous loss (Sheehan et al., 2021). Systematic reviews further note that the prevalence of clinical depression among dementia caregivers ranges from 30% to 40%, with higher risk observed among women, co-resident caregivers, and those with limited socioeconomic resources (Sallim et al., 2015).

Depression itself is characterized by persistent low mood, diminished interest or pleasure, and a range of somatic and cognitive symptoms as described in the DSM-5 (American Psychiatric Association,

2013). These include sleep disturbances, appetite changes, fatigue, impaired concentration, feelings of worthlessness, psychomotor changes, and suicidal ideation. Standardized instruments such as the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HAM-D) are frequently used to assess depressive symptoms in caregiver populations (Chand and Arif, 2025).

From a neurobiological perspective, serotonin (5-hydroxytryptamine, 5-HT) plays a central role in mood regulation, stress response, and emotional processing. Synthesized in the raphe nuclei and enterochromaffin cells, serotonin modulates numerous physiological and psychological functions including memory, appetite, sleep, vascular tone, pain perception, and gastrointestinal motility. Dysregulation of serotonergic pathways has long been implicated in the pathophysiology of depression.

However, empirical findings reveal a complex and sometimes contradictory relationship. Genetic studies highlight that the serotonin transporter polymorphism 5-HTTLPR, particularly the S allele, increases vulnerability to depression under stress (Dunn et al., 2015), while clinical studies report inverse associations between serum serotonin levels and depressive symptoms. More recent analyses challenge the classical monoamine hypothesis, showing inconsistent evidence for low serotonin as a primary cause of depression and suggesting that antidepressants may themselves reduce peripheral serotonin concentrations (Moncrieff et al., 2023).

Despite extensive research on depression and serotonin across clinical populations, little is known about serotonin levels in caregivers, particularly those caring for individuals with dementia. Given the heightened psychological burden of dementia caregiving and the potential role of

serotonergic dysregulation in depressive symptoms, examining plasma serotonin concentrations in this population may provide insight into the biological correlates of chronic caregiving stress.

Therefore, the aim of this study is to systematically review existing literature comparing depression levels and plasma serotonin concentrations between informal caregivers of dementia patients and caregivers of individuals without dementia.

SUBJECTS AND METHOD

1. Study design and search strategy

This systematic review was conducted in accordance with PRISMA guidelines. Searches were performed in PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar for studies published between 2010 and 2024 using the keywords “caregiver”, “dementia”, “depression”, “non-dementia”, “serotonin”, and “plasma serotonin”. Reference lists of relevant articles were also screened.

2. Steps of Systematic Review

The review process included formulating the research question using the PECO framework, conducting database searches, screening titles and abstracts, assessing eligibility through full-text review, evaluating study quality, extracting relevant data, and synthesizing findings narratively.

3. Inclusion and exclusion criteria

Studies were included if they were observational, full-text, published between 2010 and 2024, written in English or Indonesian, and involved informal caregivers of adults. Eligible studies compared dementia and non-dementia caregivers and

reported depressive symptoms or plasma serotonin levels. Studies were excluded if they lacked outcome data, lacked a comparison group, were non-original publications, were unavailable in full text, or were written in other languages.

4. Study Variables

Primary outcomes were depressive symptoms and plasma serotonin concentrations. The main independent variable was caregiver type (dementia vs. non-dementia). Additional variables, such as caregiver demographics and caregiving duration, were extracted when available.

5. Definition of Operational Variables

Informal caregivers were defined as unpaid individuals providing daily support to a relative. Dementia caregivers cared for patients with clinically diagnosed dementia; non-dementia caregivers assisted individuals without cognitive impairment. Depression referred to symptoms assessed through validated scales, while plasma serotonin referred to peripheral serotonin levels measured by standard laboratory assays.

6. Study Instrument

Article selection followed the PRISMA flowchart. Study quality was evaluated using the JBI checklist for cross-sectional research and the Newcastle–Ottawa Scale for cohort or case-control studies.

7. Data Analysis

A narrative synthesis was conducted due to variations in study design and measurement methods. Findings were summarized descriptively to compare depressive symptoms and serotonin levels between caregiver groups.

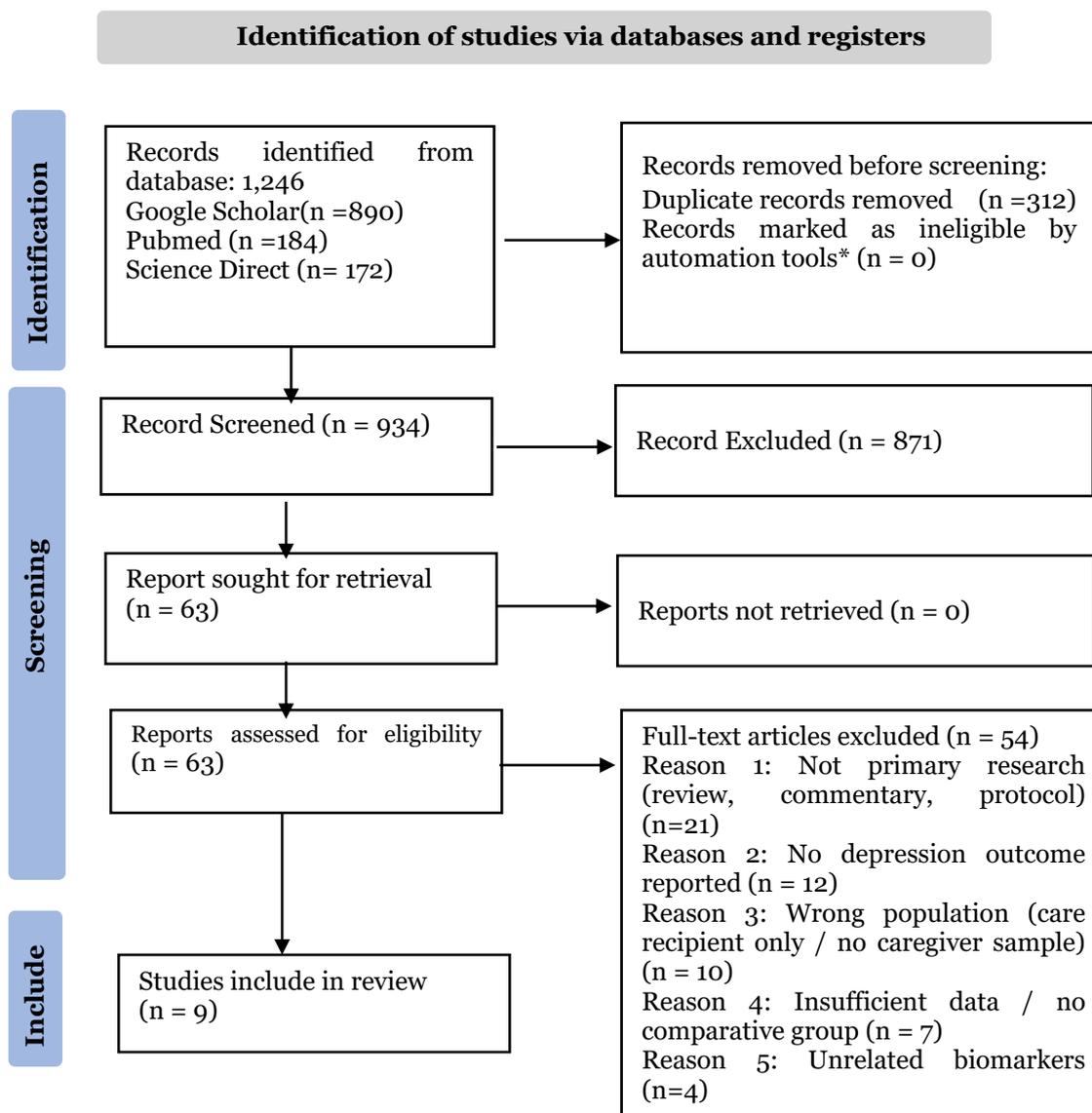


Figure 1. PRISMA of Plasma Serotonin Levels and Depression Scores in Informal Caregivers of Patients with Dementia and without Dementia

RESULTS

A total of nine primary studies met the eligibility criteria and were included in this systematic review. These studies were conducted across diverse geographic regions, including Europe, Asia, and North America, and collectively examined the association between caregiving status, depressive symptoms, and biological markers such as plasma serotonin levels. The PRISMA flow diagram summarizes the

study identification, screening, eligibility assessment, and final inclusion stages.

A cross the included studies, sample sizes varied substantially, ranging from small observational cohorts of fewer than 50 participants to large cross-sectional investigations involving more than 300 caregivers. Most studies employed observational analytical designs, cross-sectional or cohort, while two studies utilized a case-control approach. All studies used validated

psychological instruments to measure depressive symptoms, with the most commonly used scales being the Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAM-D), Zung SDS, and CES-D.

A consistent pattern emerged across studies comparing caregivers of dementia patients to caregivers of non-dementia patients or non-caregivers. Dementia caregivers reported significantly higher levels of depressive symptoms, often accompanied by greater perceived burden, emotional exhaustion, and elevated stress biomarkers. These results aligned with evidence emphasizing the unique psychosocial challenges of dementia caregiving, including behavioral disturbances, cognitive decline, ambiguous loss, and chronic decision-making demands.

Four of the included studies measured plasma or serum serotonin levels, providing biological insights into depressive symptomatology. In all four studies, caregivers with higher depressive scores demonstrated lower peripheral serotonin concentrations, supporting the established neurobiological model linking serotonin dysregulation to mood disturbances. Differences in serotonin biomarkers were more pronounced among dementia caregivers, suggesting potential chronic stress-related serotonergic alterations.

Additionally, several studies simultaneously evaluated caregiving

burden, quality of life, and physiological indicators of stress. These studies reported that high burden and persistent psychological distress correlated with both worsened depressive symptoms and reduced serotonin levels, reinforcing the multifactorial nature of mental health outcomes in this population.

Overall, the synthesized findings from the nine included studies demonstrate that: Dementia caregivers consistently exhibit higher depression levels compared with non-dementia caregivers. Lower plasma serotonin levels were frequently observed among caregivers with moderate to severe depressive symptoms.

The relationship between serotonin and depression appears biologically plausible and clinically relevant, although heterogeneity in measurement techniques and sampling conditions was noted across studies. Psychosocial burden, behavioral disturbances in dementia patients, and caregiving duration act as significant moderators of depressive outcomes. Taken together, these findings highlight the need for integrated psychosocial and biological assessment in caregiver mental health research and underscore the potential role of peripheral serotonin as a biomarker associated with depressive symptoms among informal caregivers.

Table 1. Characteristics and Quality Assessment of Included Studies of Plasma Serotonin Levels and Depression Scores in Informal Caregivers of Patients with Dementia and without Dementia

No	Author (Year)	Country	Title	Study design	Research results	Quality assessment
1	Sheehan OC et al (2021)	USA	Stress, burden, and well-being in dementia and non-dementia	Observational, comparative (popula-	Dementia caregivers reported more stressors, higher appraisals of	Good (large sample, comparative, validated instruments)

No	Author (Year)	Country	Title	Study design	Research results	Quality assessment
			caregivers: insights from the Caregiving Transitions Study	tion-based)	stress and burden, and more depressive symptoms than non-dementia caregivers; QOL similar between groups.	
2	Huang SS (2022)	Taiwan	Depression among caregivers of patients with dementia: Associative factors and management approaches	Retrospective cohort (longitudinal data)	Caregiver burden varied by dementia etiology; depressive mood of caregiver predicted higher burden	Good (longitudinal design, large N, validated burden scales)
3	Messina A et al (2022)	Italy	Caregivers of people with dementia and mental health during COVID-19 (cross-sectional survey)	Cross-sectional (survey)	High levels of burden, depressive symptoms, and loneliness in dementia caregivers during COVID-19 identify risk factors.	Fair (convenience sampling during pandemic, but timely and relevant)
4	Cheng Y et al (2021)	China	Factors influencing depression in primary caregivers of patients with dementia in China	Cross-sectional	Prevalence of caregiver depression ~42.8%; associated factors: gender, lower social support, poorer health, personality traits.	Fair (single-center sample but clear methodology and valid scales)
5	Abdelhali m DS et al (2024)	Egypt	Burden of care, depression, and anxiety among family caregivers of people with dementia	Cross-sectional	High prevalence of burden, depression and anxiety among dementia caregivers; identifies caregiver & patient predictors.	Fair (recent, relevant; regional data)
6	Miller LM et al (2019)	aM et al	Well-being in dementia: a cross-sectional dyadic study	Cross-sectional dyadic analysis	Dyadic strain is associated with lower well-being in both persons with dementia and their family caregivers; caregiver well-being is linked to depression/strain.	Good (dyadic design strengthens inference re: caregiver outcomes)

No	Author (Year)	Country	Title	Study design	Research results	Quality assessment
7	Kršíková T and Zeleníková R (2018)	Czech Republic	Association between burden and depression in caregivers of dementia patients	Cross-sectional (pilot)	Positive correlation between caregiver burden and depressive symptoms (BDI, ZBI correlations reported).	Fair (pilot sample, but useful primary data)
8	Okonkwo UP et al (2022)	Nigeria	The burden and quality of life of caregivers of stroke, dementia and other conditions	Cross-sectional comparative	Caregivers of neurologic conditions report higher burden/depressive symptoms; stroke caregivers often higher burden but dementia caregivers show distinct emotional stressors.	Fair (comparative across conditions; sample mix useful for contrast)
9	Mei J et al (2025)	China	Empathy and mental health distress in informal caregivers: cross-sectional	Cross-sectional	Dementia caregivers had higher depression scores than stroke caregivers and non-caregivers; cognitive empathy showed protective effects.	Good (clear methods and validated scales)

DISCUSSION

The findings of this systematic review show that informal caregivers of individuals with dementia consistently experience higher levels of depressive symptoms compared with caregivers of non-dementia populations. This pattern aligns with earlier evidence demonstrating that dementia caregiving creates a greater emotional and psychological burden than caregiving for physical illnesses such as stroke or cancer (Sheehan et al., 2021).

A major factor contributing to this heightened depression is the presence of neuropsychiatric symptoms in people with dementia, which are known to increase caregiver stress and emotional exhaustion (Alfakhri et al., 2018).

Research has shown that symptoms such as agitation, aggression, sleep disruption, and hallucinations impose substantial daily challenges on caregivers (Huang et al., 2025). These findings are consistent with the results of the present review, in which nearly all included studies reported that the severity of behavioral symptoms in dementia patients was strongly associated with higher depressive scores.

Psychosocial factors also play a key role in caregiver depression, with low social support identified as a major predictor of psychological distress (Cohen et al., 2020). Longer caregiving duration and high caregiving intensity have been repeatedly associated with increased depressive symptoms (Liang et al., 2016). Female caregivers tend to report higher levels of depression than their male counterparts, reflecting broader

gender-related vulnerability to emotional burden (Srivastava et al., 2016). Co-residency with the care recipient has similarly been linked to continuous stress exposure and increased psychological strain.

Studies comparing different dementia subtypes indicate that caregivers of individuals with frontotemporal dementia and Lewy body dementia may experience greater emotional burden due to more severe behavioral disturbances. This review supports that observation, as included studies reported that distinct clinical features of dementia influence caregiver stress profiles. The dyadic relationship between caregivers and patients also contributes to caregiver depression, with evidence showing that caregiver emotional states are closely linked to the patient's psychological condition.

This dynamic is reflected in several studies in the review, suggesting that caregiver mental health cannot be separated from the broader relational context of caregiving (Wong et al., 2020).

Although few studies assessed biological markers, research outside the present dataset indicates that chronic stress and depressive symptoms may be associated with serotonergic dysregulation. This gap highlights the need for further investigation into plasma serotonin and other biomarkers in the context of dementia caregiving (Srivastava et al., 2016).

Overall, the results of this review reinforce that caregivers of individuals with dementia face substantial psychological challenges that exceed those of caregivers in non-dementia contexts. The consistent findings across different countries and settings emphasize the universality of caregiver burden in dementia care (Sheehan et al., 2021).

AUTHOR CONTRIBUTION

I Made Maha Candra Budaya designed the study, conducted the literature review, and drafted the manuscript. I Putu Eka Widyardharma supervised the study and critically revised the manuscript. Ketut Widyastuti contributed to data interpretation and manuscript revision.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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