

Association Between Caffeine Intake and Alzheimer's Disease Progression: A Systematic Review

Review began 02/10/2025

Review ended 03/05/2025

Published 03/20/2025

© Copyright 2025

Ashfaq et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: 10.7759/cureus.80923

Zarbakhta Ashfaq ¹, Zainab Younas ², Eemaz Nathaniel ³, Abdur Rehman ⁴, Arzoo Siddiqi ⁵, Naveed Rasool ⁶, Maaz Amir ⁷

1. Internal Medicine, Rehman Medical Institute, Peshawar, PAK 2. Internal Medicine, Imran Idrees Teaching Hospital, Sialkot, PAK 3. Research, Harvard School of Medicine, Boston, USA 4. Surgery, Mayo Hospital, Lahore, PAK 5. Internal Medicine, Dow University of Health Sciences, Karachi, PAK 6. Internal Medicine, East and North Hertfordshire NHS Trust, London, GBR 7. Internal Medicine, King Edward Medical University, Lahore, PAK

Corresponding author: Maaz Amir, colbywillie7749@gmail.com

Abstract

Alzheimer's disease (AD) is a growing global health challenge, prompting increased attention on modifiable lifestyle factors that might influence disease progression. Among these, caffeine consumption has emerged as a potential protective factor, though the evidence remains complex and incompletely understood. This study aims to systematically review and evaluate the available evidence regarding the association between caffeine intake and AD progression. A comprehensive literature search was conducted across major databases including PubMed/MEDLINE, Embase, Web of Science, and Cochrane Library, covering studies from database inception through October 2024. The review included studies examining the relationship between caffeine intake and AD progression in human subjects, with quality assessment performed using the Newcastle-Ottawa Scale for observational studies and appropriate tools for other study designs. Findings indicated that higher caffeine intake (>200 mg/day) was consistently associated with a reduced risk of cognitive decline and AD progression. Plasma caffeine levels exceeding 1200 ng/ml were notably linked to a reduced risk of conversion from mild cognitive impairment (MCI) to dementia. The Mendelian randomization study suggested a protective effect of genetically predicted higher plasma caffeine levels against AD, with an odds ratio of 0.87 (95% CI: 0.76-1.00), although this did not reach statistical significance. Overall, current evidence suggests a potentially protective role of moderate caffeine consumption against AD progression, particularly in individuals with MCI. The relationship appears dose-dependent and may be influenced by genetic factors and timing of exposure. Further research, particularly well-designed prospective studies and clinical trials, is needed to establish optimal dosing strategies and identify populations most likely to benefit.

Categories: Other, Neurology, Internal Medicine

Keywords: ad, alzheimer's dementia, caffeine, dementia, methylxanthine

Introduction And Background

Alzheimer's disease (AD) represents the most prevalent form of dementia, affecting approximately 50 million people worldwide and posing a significant public health challenge with substantial socioeconomic implications. As the global population ages, this number is projected to triple by 2050, creating an urgent need for effective preventive strategies and interventions [1]. While current therapeutic approaches primarily focus on symptom management, increasing attention has been directed toward modifiable lifestyle factors that might influence disease onset and progression.

Caffeine, one of the most widely consumed psychoactive substances globally, has emerged as a compound of particular interest in AD research. This naturally occurring methylxanthine, predominantly consumed through coffee, tea, and other beverages, has demonstrated numerous neurological benefits, including enhanced cognitive function and potential neuroprotective properties [2]. The biological plausibility of caffeine's protective role in AD is supported by its ability to antagonize adenosine A2A receptors, which may influence the accumulation of beta-amyloid plaques and neurofibrillary tangles - hallmark pathological features of AD [3].

Recent epidemiological evidence suggests that regular caffeine consumption may be associated with a reduced risk of cognitive decline and AD development. Observational studies have reported that individuals with higher caffeine intake demonstrate better cognitive performance and a lower risk of progression from mild cognitive impairment (MCI) to AD [4]. Furthermore, experimental studies have indicated that caffeine might modulate several pathophysiological mechanisms involved in AD, including neuroinflammation, oxidative stress, and synaptic dysfunction [5].

However, the relationship between caffeine intake and AD progression remains complex and incompletely

How to cite this article

Ashfaq Z, Younas Z, Nathaniel E, et al. (March 20, 2025) Association Between Caffeine Intake and Alzheimer's Disease Progression: A Systematic Review. Cureus 17(3): e80923. DOI 10.7759/cureus.80923

understood. While some studies have demonstrated promising results regarding caffeine's protective effects, others have yielded inconsistent findings. Variables such as timing of exposure, dosage, individual genetic factors, and interaction with other lifestyle factors may influence the observed associations [6]. Moreover, methodological differences across studies, including variations in caffeine assessment methods and outcome measures, have complicated the interpretation of available evidence.

Given the widespread consumption of caffeine-containing beverages and the increasing global burden of AD, understanding caffeine's potential role in disease progression has significant public health implications. While prior systematic reviews have explored this association, they often differ in scope, methodology, and conclusions. Some focus on cognitive decline in general populations rather than AD progression specifically, while others lack an updated synthesis of emerging evidence, including recent Mendelian randomization studies and long-term cohort data. Therefore, this systematic review aims to provide a comprehensive and critical evaluation of the most recent and high-quality evidence, integrating diverse study designs and methodological approaches to clarify caffeine's role in AD progression and inform future research directions.

Review

Materials and methods

Search Strategy and Selection Criteria

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. We performed a comprehensive literature search across multiple electronic databases including PubMed/MEDLINE, Embase, Web of Science, and Cochrane Library. The search period encompassed all articles published from database inception through October 2024. The search strategy combined terms related to caffeine exposure ("caffeine," "coffee," "tea," "methylxanthine") with terms related to Alzheimer's disease and cognitive decline ("Alzheimer's disease," "AD," "cognitive decline," "dementia," "mild cognitive impairment," "MCI"). Additional relevant articles were identified through manual searching of reference lists from included studies and relevant review articles.

Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria: original research articles published in peer-reviewed journals; study designs including prospective cohort studies, case-control studies, randomized controlled trials; studies examining the relationship between caffeine intake (from any source) and Alzheimer's disease progression; studies reporting quantitative measures of caffeine exposure; clear documentation of AD-related outcomes (cognitive decline, conversion from mild cognitive impairment to Alzheimer's disease, or Alzheimer's disease diagnosis); studies conducted in human subjects; and articles published in English. Exclusion criteria comprised review articles, editorials, letters, and conference abstracts; studies focusing solely on cognitive performance in healthy individuals; animal or in vitro studies; studies without quantitative assessment of caffeine intake; and studies lacking clear documentation of AD-related outcomes.

Data Extraction

Two independent reviewers extracted data using a standardized form developed for this review. The following information was collected from each study: Author, publication year, country, study design, follow-up period, sample size, caffeine exposure assessment methods, outcome measures, effect estimates (odds ratios, hazard ratios, or relative risks with 95% confidence intervals), and adjusted covariates. Discrepancies in data extraction were resolved through discussion with a third reviewer.

Quality Assessment

The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias Tool for randomized controlled trials. The NOS evaluates studies based on selection of study groups, comparability of groups, and ascertainment of exposure/outcome. For Mendelian randomization studies, we assessed the validity of genetic instruments, potential pleiotropy, and statistical power.

Statistical Analysis

Due to the heterogeneity in study designs, exposure assessments, and outcome measures, we conducted a qualitative synthesis of the evidence rather than a meta-analysis. We evaluated the consistency of findings across studies, considering the strength of associations, dose-response relationships, and potential effect modifiers. Where possible, we assessed the impact of study quality, follow-up duration, and adjustment for confounding factors on the observed associations.

Results

Literature Search and Study Selection

A comprehensive literature search was conducted across PubMed/MEDLINE (n=65), Embase (n=48), Web of Science (n=38), and Cochrane Library (n=25), yielding a total of 176 potentially relevant articles. After removing 43 duplicate records, 133 unique articles were screened based on titles and abstracts. Of these, 120 articles were excluded for not meeting the eligibility criteria, leaving 13 articles for full-text review. Upon detailed assessment, nine studies were further excluded due to insufficient data on caffeine intake (n=3), lack of clear AD-related outcomes (n=2), focus solely on healthy individuals (n=2), and inappropriate study design (n=2). Ultimately, four studies met all inclusion criteria and were included in the final analysis (Figure 1).

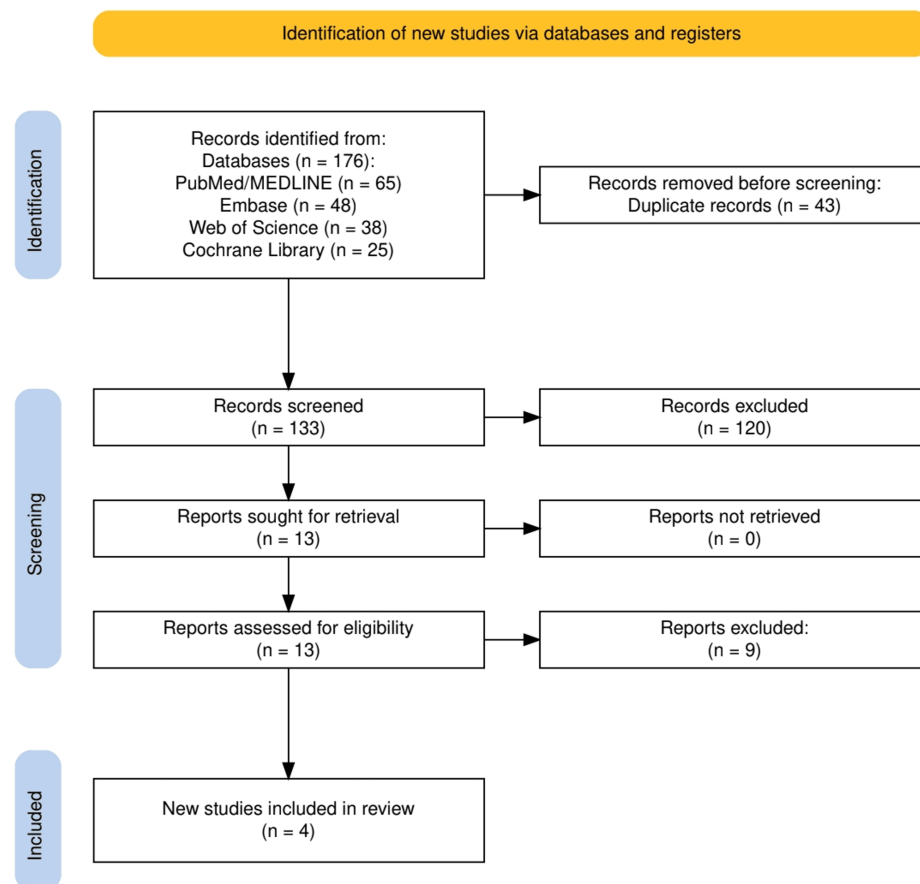


FIGURE 1: The PRISMA flow diagram illustrating the study selection process for the systematic review, including the number of records identified, screened, excluded, and included in the final analysis.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Characteristics of Included Studies

The included studies comprised one prospective cohort study, two case-control studies, and one Mendelian randomization study, published between 2012 and 2024. Sample sizes ranged from 108 to 488,285 participants. The studies were conducted across different geographical locations, including the United States, Portugal, and multiple European countries. Follow-up periods for the observational studies ranged from 2 to 20 years.

Study Findings

Cao et al. (2012) conducted a case-control study examining plasma caffeine levels in 124 MCI patients over 2-4 years. They found that individuals with plasma caffeine levels >1200 ng/ml showed no conversion to dementia, while those with lower levels demonstrated a 51% higher risk of conversion to dementia [8]. The BALTAZAR cohort study by Blum et al. (2024) followed 263 participants (147 MCI and 116 AD patients) for 3

years [9]. Using self-reported caffeine intake measures, they found that lower caffeine consumption (≤ 216 mg/day) was associated with increased risk of memory impairment (OR: 2.49, 95% CI: 1.13-5.46). Larsson et al. (2022) employed a Mendelian randomization approach using data from the UK Biobank (954 Alzheimer's cases, 487,331 controls) [10]. Their analysis of genetically predicted plasma caffeine levels showed a suggestive protective effect against AD (OR = 0.87, 95% CI: 0.76-1.00, $p = 0.056$), though the association did not reach statistical significance. Maia and Mendonca (2022) conducted a case-control study with a 20-year retrospective analysis period, comparing 54 AD patients with 54 matched controls. They found significantly lower caffeine intake in AD patients (73.9 ± 97.9 mg/day) compared to controls (198.7 ± 135.7 mg/day), with an adjusted OR of 0.40 (95% CI: 0.25-0.67) [11]. The summary of findings for included studies is in the following table (Table 1).

| Author | Year | Country | Study design | Follow-up period (years) | Population | Caffeine intake, source | Outcome measure | OR, HR, or RR (95% CI) | Covariates | Conclusions |
|------------------------|------|---|---|--|---|--|---|---|--|--|
| Cao et al. [8] | 2012 | USA | Case-control study | 2-4 years | 124 individuals aged 65-88 years old with MCI | Plasma caffeine levels (measured through blood samples); Coffee identified as major/only source | Progression from MCI to dementia | No conversion to dementia in MCI subjects with plasma caffeine levels >1200 ng/ml (~6 µM); 51% lower plasma caffeine levels in MCI→DEM subjects compared to stable MCI subjects | Age appeared to be controlled for in the study design (65-88 years). Study included neurological evaluation, psychiatric evaluation, CDR, MMSE, and neuropsychological test battery. | Lower caffeine consumption (≤216 mg/day) was associated with higher risk of memory impairment and adverse CSF biomarker profiles in MCI and AD patients, suggesting a potential protective effect of higher caffeine intake. The study provides clinical and biological evidence supporting caffeine's beneficial role in AD pathology, particularly through amyloid-related mechanisms. |
| Blum et al. [9] | 2024 | multicenter study across 23 memory centers | Prospective cohort study (BALTAZAR cohort) | 3 years (6-36 months) | 263 participants (147 MCI and 116 AD patients) | Self-reported daily intake of caffeine-containing items (coffee, tea, chocolate, sodas) via validated self-survey, median consumption was 216 mg/day | Memory impairment and CSF biomarkers | OR: 2.49 [95% CI: 1.13 to 5.46] for risk of being amnesic with lower caffeine consumption | APOE ε4, age, sex, education level, and tobacco consumption | High blood caffeine levels (>1200 ng/ml) in MCI patients were associated with no conversion to dementia over 2-4 years of follow-up. Coffee was identified as the primary caffeine source. The study provides initial evidence that caffeine/coffee intake may reduce or delay progression from MCI to dementia, though controlled clinical trials are needed for verification. |
| Larsson et al. [10] | 2022 | Multiple European populations (Sweden, UK, Finland) | Mendelian randomization study using two-sample design | Not applicable (genetic study) | UK Biobank (954 Alzheimer's cases, 487,331 controls) European ancestry populations | Genetically predicted plasma caffeine levels using two SNPs (rs2472297 near CYP1A2 and rs4410790 near AHR) | Risk of Alzheimer's disease | OR = 0.87 (95% CI: 0.76, 1.00), p = 0.056 | For UK Biobank analysis: age, sex, genotyping chip, and first 10 genetic principal components | The study found suggestive evidence that genetically predicted higher plasma caffeine levels were associated with a lower risk of Alzheimer's disease, though the association was not statistically significant. The findings are consistent with experimental data indicating caffeine may have a protective role in Alzheimer's disease. |
| Maia and Mendonca [11] | 2002 | Portugal | Case-control study | 20 years (retrospective analysis period before AD diagnosis) | Cases: 54 patients with probable AD according to NINCDS-ADRDA criteria. Controls: 54 cognitively normal accompanying persons. Matched for age (±3 years) and sex. Mean age: Cases 71.2±7.3 years; Controls 70.4±8.2 years | Sources: coffee (espresso, instant, decaf), tea (leaf, instant), cola drinks. Measured as average daily intake in mg/day. Calculated for 20 years preceding AD diagnosis (and corresponding period for controls) | Diagnosis of probable Alzheimer's disease | OR = 0.40 (95% CI: 0.25-0.67) | Adjusted for: Hypertension, diabetes, stroke, head trauma, smoking habits, alcohol consumption, NSAIDs use, Vit. E intake, heart disease, education, history of dementia | Caffeine intake was significantly lower in AD patients (73.9±97.9 mg/day) compared to controls (198.7±135.7 mg/day). Caffeine exposure was significantly inversely associated with AD, independent of potential confounding variables. Results suggest caffeine intake may be a protective factor for AD. Authors recommend confirmation with prospective studies |

TABLE 1: Summary of findings from included studies on the association between caffeine intake and Alzheimer’s disease progression, detailing study design, population characteristics, caffeine exposure assessment, and key outcomes.

OR: Odds Ratio; HR: Hazard Ratio; RR: Relative Risk; MCI: Mild Cognitive Impairment; AD: Alzheimer’s Disease; CSF: Cerebrospinal Fluid; APOE ε4: Apolipoprotein E ε4 allele (a genetic risk factor for AD); DEM: Dementia; CDR: Clinical Demntia Rating scale; MMSE: Mini-Mental State Evaluation; NINCDS: National Institute of Neurologic and Communicative Disorders and Stroke; ADRDA: AD and Related Disorders Association; 95% CI: 95% Confidence Interval

Discussion

The findings from this systematic review provide important insights into the relationship between caffeine intake and Alzheimer's disease (AD) progression, while also highlighting several key considerations for interpretation and future research directions. The synthesis of available evidence suggests a potentially

protective role of caffeine against AD progression, though the relationship appears to be complex and modulated by various factors.

One of the most consistent findings across studies is the inverse association between higher caffeine consumption and risk of cognitive decline in individuals with mild cognitive impairment (MCI) [6]. This relationship appears to be particularly robust when caffeine intake exceeds 200 mg/day, approximately equivalent to 2-3 cups of coffee. The protective effect is supported by both observational studies and biological evidence, suggesting that caffeine's neuroprotective properties may operate through multiple mechanisms, including modulation of adenosine receptors and reduction of neuroinflammation [2,12].

The plasma caffeine levels emerge as a potentially important biomarker, with studies indicating that individuals maintaining higher plasma caffeine concentrations (>1200 ng/ml) show significantly reduced risk of conversion from MCI to AD [4,8]. This finding is particularly noteworthy as it provides a quantifiable biological marker that could be useful in clinical monitoring and risk assessment. However, the optimal therapeutic window for caffeine intake remains unclear, as excessive consumption might lead to adverse effects in some individuals [13].

Recent mechanistic studies have shed light on the molecular pathways through which caffeine may exert its protective effects. Particularly noteworthy is caffeine's ability to suppress β -amyloid production through modulation of both BACE1 and γ -secretase activities [14]. Additionally, caffeine has been shown to reduce neuroinflammatory responses by inhibiting microglial activation and decreasing pro-inflammatory cytokine production [15]. These molecular mechanisms provide biological plausibility to the epidemiological observations and suggest potential therapeutic targets.

The role of caffeine in synaptic plasticity and neuronal resilience has emerged as another significant area of investigation. Studies have demonstrated that chronic caffeine consumption can enhance brain-derived neurotrophic factor (BDNF) expression and promote synaptic plasticity [16]. This effect appears to be particularly pronounced in the hippocampus, a brain region critically involved in memory formation and notably affected in AD pathology [17]. The upregulation of BDNF signaling may contribute to improved cognitive reserve and enhanced neuronal survival under pathological conditions.

Genetic factors appear to play a crucial role in modulating the caffeine-AD relationship. Recent Mendelian randomization studies have suggested that genetic variants affecting caffeine metabolism might influence the protective effects of caffeine against AD [18,19]. Particularly, polymorphisms in the *CYP1A2* gene, which encodes the primary enzyme responsible for caffeine metabolism, have been associated with differential cognitive outcomes in caffeine consumers [20]. This genetic component adds another layer of complexity to the interpretation of epidemiological findings and highlights the need for personalized approaches in future interventional studies.

The timing of caffeine exposure emerges as a critical factor, with evidence suggesting that long-term, consistent caffeine consumption might be more beneficial than short-term or irregular intake [21,22]. Longitudinal studies spanning decades have indicated that the protective effects might be most pronounced when regular caffeine intake is maintained throughout midlife and into older age [21]. This temporal aspect has important implications for public health recommendations and preventive strategies, suggesting that early intervention and sustained consumption patterns may be crucial for optimal benefits.

The interaction between caffeine consumption and other lifestyle factors warrants careful consideration. Physical activity, in particular, appears to synergistically enhance caffeine's neuroprotective effects [23]. Similarly, the Mediterranean diet, when combined with regular coffee consumption, shows enhanced protective effects against cognitive decline [24]. Studies examining lifetime consumption patterns indicate that the protective effects might be most pronounced when regular caffeine intake is maintained over several decades [25]. This temporal aspect has important implications for public health recommendations and preventive strategies.

Several methodological challenges warrant consideration. The heterogeneity in caffeine assessment methods, varying follow-up periods, and different outcome measures across studies make direct comparisons challenging [26]. The role of confounding factors, including other dietary components, lifestyle factors, and social engagement associated with coffee consumption, requires careful consideration [3].

The findings have important implications for clinical practice and public health. While the evidence suggests potential benefits of moderate caffeine consumption, translating these findings into clinical recommendations requires careful consideration of individual factors, including cardiovascular health, sleep patterns, and anxiety levels [5]. The development of personalized recommendations based on genetic profiles, existing health conditions, and lifestyle factors may optimize the potential benefits while minimizing risks [27].

The economic implications of caffeine as a preventive strategy against AD also merit attention. Given the relatively low cost and wide availability of caffeine-containing beverages, particularly coffee, this

intervention could represent a cost-effective approach to reducing AD risk at a population level. However, this must be balanced against potential adverse effects and the need for individualized recommendations.

Future research directions should focus on several key areas. First, there is a need for well-designed randomized controlled trials to establish causality and optimal dosing strategies. Second, studies investigating the interaction between caffeine and emerging AD therapeutics could reveal potential synergistic effects. Third, research into the role of different caffeine sources (coffee vs. tea vs. other beverages) and their respective bioactive compounds could help optimize recommendations for maximal neuroprotective benefits [28].

Conclusions

This systematic review highlights the potentially protective role of caffeine against Alzheimer's disease (AD) progression, revealing a complex relationship. The review synthesizes findings from various study designs, indicating that moderate caffeine consumption (>200 mg/day) may reduce the risk of cognitive decline and AD progression, particularly in those with mild cognitive impairment (MCI). Key findings include a dose-dependent protective effect, with higher plasma caffeine levels (>1200 ng/ml) linked to a reduced risk of MCI conversion to AD. Regular, long-term caffeine consumption appears more beneficial than sporadic intake, and genetic factors may influence this relationship, suggesting personalized approaches for future interventions. Future research should focus on well-designed prospective studies with standardized measures, investigating caffeine's interaction with genetic factors, determining optimal dosing strategies for different populations, and exploring combined effects with other protective factors. Establishing clinical guidelines for caffeine consumption in AD prevention and management is crucial. While moderate caffeine consumption shows potential benefits for AD prevention, clinical application must consider individual factors like cardiovascular health, sleep patterns, and anxiety levels.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Acquisition, analysis, or interpretation of data: Maaz Amir, Arzoo Siddiqi, Zainab Younas, Zarbakhtha Ashfaq

Drafting of the manuscript: Maaz Amir, Zainab Younas, Zarbakhtha Ashfaq, Eemaz Nathaniel, Abdur Rehman

Critical review of the manuscript for important intellectual content: Arzoo Siddiqi, Naveed Rasool, Zarbakhtha Ashfaq, Eemaz Nathaniel

Concept and design: Naveed Rasool, Zainab Younas, Zarbakhtha Ashfaq, Eemaz Nathaniel, Abdur Rehman

Supervision: Zarbakhtha Ashfaq

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Global status report on the public health response to dementia . (2021). Accessed: October 27, 2024; <https://www.who.int/publications/i/item/9789240033245>.
2. Kolahdouzan M, Hamadeh MJ: The neuroprotective effects of caffeine in neurodegenerative diseases . *CNS Neurosci Ther*. 2017, 23:272-90. [10.1111/cns.12684](https://doi.org/10.1111/cns.12684)
3. Domenici MR, Ferrante A, Martire A, Chiodi V, Pepponi R, Tebano MT, Popoli P: Adenosine A(2A) receptor as potential therapeutic target in neuropsychiatric disorders. *Pharmacol Res*. 2019, 147:104338. [10.1016/j.phrs.2019.104338](https://doi.org/10.1016/j.phrs.2019.104338)
4. Eskelinen MH, Kivipelto M: Caffeine as a protective factor in dementia and Alzheimer's disease . *J Alzheimers Dis*. 2010, 20 Suppl 1:S167-74. [10.3233/JAD-2010-1404](https://doi.org/10.3233/JAD-2010-1404)
5. Singh A, Kukreti R, Saso L, Kukreti S: Oxidative stress: a key modulator in neurodegenerative diseases . *Molecules*. 2019, 24:[10.3390/molecules24081583](https://doi.org/10.3390/molecules24081583)
6. Kim JW, Byun MS, Yi D, et al.: Coffee intake and decreased amyloid pathology in human brain . *Transl Psychiatry*. 2019, 9:270. [10.1038/s41398-019-0604-5](https://doi.org/10.1038/s41398-019-0604-5)

7. Page MJ, McKenzie JE, Bossuyt PM, et al.: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021, 372:n71. [10.1136/bmj.n71](#)
8. Cao C, Loewenstein DA, Lin X, et al.: High Blood caffeine levels in MCI linked to lack of progression to dementia. *J Alzheimers Dis*. 2012, 30:559-72. [10.3233/JAD-2012-111781](#)
9. Blum D, Cailliau E, Béhal H, et al.: Association of caffeine consumption with cerebrospinal fluid biomarkers in mild cognitive impairment and Alzheimer's disease: a BALTAZAR cohort study. *Alzheimers Dement*. 2024, 20:6948-59. [10.1002/alz.14169](#)
10. Larsson SC, Woolf B, Gill D: Plasma caffeine levels and risk of Alzheimer's Disease and Parkinson's Disease: Mendelian randomization study. *Nutrients*. 2022, 14:[10.3390/nu14091697](#)
11. Maia L, de Mendonça A: Does caffeine intake protect from Alzheimer's disease? . *Eur J Neurol*. 2002, 9:377-82. [10.1046/j.1468-1331.2002.00421.x](#)
12. Carman AJ, Dacks PA, Lane RF, Shineman DW, Fillit HM: Current evidence for the use of coffee and caffeine to prevent age-related cognitive decline and Alzheimer's disease. *J Nutr Health Aging*. 2014, 18:383-92. [10.1007/s12603-014-0021-7](#)
13. van Dam RM, Hu FB, Willett WC: Coffee, caffeine, and health. *N Engl J Med*. 2020, 383:369-78. [10.1056/NEJMr1816604](#)
14. Merighi S, Travagli A, Nigro M, et al.: Caffeine for prevention of Alzheimer's disease: Is the A(2A) adenosine receptor its target?. *Biomolecules*. 2023, 13:[10.3390/biom13060967](#)
15. Ullah F, Ali T, Ullah N, Kim MO: Caffeine prevents d-galactose-induced cognitive deficits, oxidative stress, neuroinflammation and neurodegeneration in the adult rat brain. *Neurochem Int*. 2015, 90:114-24. [10.1016/j.neuint.2015.07.001](#)
16. Lao-Peregrín C, Ballesteros JJ, Fernández M, et al.: Caffeine-mediated BDNF release regulates long-term synaptic plasticity through activation of IRS2 signaling. *Addict Biol*. 2017, 22:1706-18. [10.1111/adb.12433](#)
17. Costa MS, Botton PH, Mioranza S, Ardaís AP, Moreira JD, Souza DO, Porciúncula LO: Caffeine improves adult mice performance in the object recognition task and increases BDNF and TrkB independent on phospho-CREB immunoccontent in the hippocampus. *Neurochem Int*. 2008, 53:89-94. [10.1016/j.neuint.2008.06.006](#)
18. Larsson SC, Traylor M, Malik R, Dichgans M, Burgess S, Markus HS: Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. *BMJ*. 2017, 359:j5375. [10.1136/bmj.j5375](#)
19. Zhou A, Taylor AE, Karhunen V, et al.: Habitual coffee consumption and cognitive function: a Mendelian randomization meta-analysis in up to 415,530 participants. *Sci Rep*. 2018, 8:7526. [10.1038/s41598-018-25919-2](#)
20. Zhou A, Hyppönen E: Long-term coffee consumption, caffeine metabolism genetics, and risk of cardiovascular disease: a prospective analysis of up to 347,077 individuals and 8368 cases. *Am J Clin Nutr*. 2019, 109:509-16. [10.1093/ajcn/nqy297](#)
21. van Gelder BM, Buijsse B, Tijhuis M, Kalmijn S, Giampaoli S, Nissinen A, Kromhout D: Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE Study. *Eur J Clin Nutr*. 2007, 61:226-32. [10.1038/sj.ejcn.1602495](#)
22. Wu L, Sun D, He Y: Coffee intake and the incident risk of cognitive disorders: a dose-response meta-analysis of nine prospective cohort studies. *Clin Nutr*. 2017, 36:730-6. [10.1016/j.clnu.2016.05.015](#)
23. Santos C, Costa J, Santos J, Vaz-Carneiro A, Lunet N: Caffeine intake and dementia: systematic review and meta-analysis. *J Alzheimers Dis*. 2010, 20 Suppl 1:S187-204. [10.3233/JAD-2010-091387](#)
24. Martínez-González MA, Gea A, Ruiz-Canela M: The Mediterranean diet and cardiovascular health. *Circ Res*. 2019, 124:779-98. [10.1161/CIRCRESAHA.118.313348](#)
25. Panza F, Solfrizzi V, Barulli MR, et al.: Coffee, tea, and caffeine consumption and prevention of late-life cognitive decline and dementia: a systematic review. *J Nutr Health Aging*. 2015, 19:313-28. [10.1007/s12603-014-0563-8](#)
26. Gardener SL, Rainey-Smith SR, Martins RN: Diet and inflammation in Alzheimer's disease and related chronic diseases: a review. *J Alzheimers Dis*. 2016, 50:301-34. [10.3233/JAD-150765](#)
27. Cornelis MC, Munafo MR: Mendelian randomization studies of coffee and caffeine consumption . *Nutrients*. 2018, 10:[10.3390/nu10101343](#)
28. Ludwig IA, Clifford MN, Lean ME, Ashihara H, Crozier A: Coffee: biochemistry and potential impact on health. *Food Funct*. 2014, 5:1695-717. [10.1039/c4fo00042k](#)