Is caffeine a potential therapeutic intervention for Alzheimer's disease?

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Ying Zhai[1], Y Mukish M Yelanchezian[2], Andrea Kwakowsky[1, 2, *]

1 Discipline of Pharmacology and Therapeutics, School of Medicine, College of Medicine, Nursing and Health Sciences, Galway Neuroscience Centre, University of Galway, Galway, Ireland

2 Centre for Brain Research, Department of Anatomy and Medical Imaging, Faculty of Medical and Health Science, University of Auckland, Auckland, New Zealand

*Correspondence to: Andrea Kwakowsky, andrea.kwakowsky@universityofgalway.ie.

Abstract

Caffeine is the most commonly used stimulant drug in the world. Increasing evidence has indicated that caffeine may have a neuroprotective effect in delaying the onset or treatment of several neurodegenerative disorders, especially Alzheimer's disease (AD). During the progression of AD, accelerated memory loss and cognitive decline are accompanied by two neuropathological hallmarks, the accumulation of amyloid- and tau proteins. The long incubation nature of AD before definitive diagnosis combined with extended duration of life spent with illness contribute significantly to the public health burden, as patients spend much of their end life in a state of severe disability and heavy dependence. Moreover, current drug treatments only provide marginal benefits, creating an urgent need for developing new therapeutic options. There is supportive evidence from clinical trials that caffeine has neuroprotective properties against dementia and AD, but more research is needed to strengthen and confirm these observations. This mini-review presents a short synopsis of the effect of caffeine/coffee on cognition and Alzheimer's disease by evaluating a substantial basis of clinical trials that are related to this topic.

Key words: Alzheimer's disease; caffeine; coffee; cognition; dementia

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Introduction

The pure alkaloid 1,3,7-trimethylxanthine (caffeine) is the most widely used psychostimulant in the world (Fredholm et al., 1999). With variations regarding the daily consumption of caffeine between countries, up to 400 mg per day is viewed as safe for healthy individuals according to the guidelines of the European Food Safety Authority (EFSA NDA Panel (EFSA Panel on Dietetic Products Nutrition and Allergies), 2015). Due to its hydrophobic properties, caffeine is able to freely cross all biological membranes and the blood-brain barrier (Fredholm et al., 1999; Schreiner and Popescu, 2022). 99% of caffeine from beverages, including coffee, is quickly absorbed and distributed in the body water, reaching peak plasma concentration within 15–120 minutes (Bonati et al., 1982; Arnaud, 1987). In the central nervous system, where the caffeine concentration remains similar to that in the blood, caffeine interacts with different neurotransmission pathways and thus promotes behavioral alterations, including increased energetic arousal and vigilance, reduced fatigue, and improved memory and cognition (Fredholm et al., 1999; Smit and Rogers, 2000; Rogers et al., 2003; Marzagalli and Castorina, 2015).

Alzheimer's disease (AD) is the most common type of dementia, and its incidence increases with age (Alzheimer's Association, 2022). The early stage of AD is difficult to recognize due to the endogenous compensation nature of the brain, which means neuronal loss and the consequent relentless deterioration of cognition and memory are already extensive by the point of diagnosis. The leading neuropathological hallmarks of the disease are the excessive deposition of extracellular neurotoxic amyloid-β protein (Aβ) and intracellular neurofibrillary tangles composed of hyperphosphorylated tau proteins (Alzheimer's Association, 2022). Despite over a century since the discovery of the first AD patient and efforts that has predominantly focused on developing curative treatments, all seven drugs approved by the Food and Drug Administration for AD in the United States, namely Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (Razadyne), Memantine (Namenda), Donepezil and Memantine manufactured combination (Namzaric), Aducanumab (Aduhelm), and Lecanemab (Lequembi), are unable to prevent AD onset or slow its progression (Alzheimer's Association, 2022). As mentioned above, there is an urgent need to develop more effective therapeutics.

The concept of morbidity compression, which was proposed by Professor James F. Fries (1980), emphasized that the age of onset of chronic disease may be postponed so that the burden of lifetime illness can be compressed into a shorter period before the time of death. Given the fact that chronic neurodegenerative

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diseases are more prevalent after the age of 65 years, affecting an estimated 1 in 14 people over the age of 65 years and 1 in every 6 people over the age of 80 years, delayed age at the onset of these diseases (NHS, 2021), therefore, would significantly shorten the number of years spent with morbidity. Taking into account the very limited therapeutic options available for AD, if it is too late to rescue any pathological alterations in AD cases by the time of diagnosis, it will be more feasible to delay the AD onset by dietary interventions or nutraceuticals such as caffeine. There are ample human epidemiological studies indicating that long-term moderate caffeine intake can be beneficial for memory and cognitive functions, especially during the pre-morbidity stage (Maia and de Mendonça, 2002; Corley et al., 2010; Santos et al., 2010b; Cao et al., 2012; Beydoun et al., 2014). One case-control study, which included 54 AD patients and 54 healthy controls adjusted for age (±3 years) and sex, suggesting that average daily caffeine consumption (198.7 ± 135.7 mg in controls *vs.* 73.9 ± 97.9 mg in AD patients) has a significant inverse association with AD (odds ratio (OR): 0.40, 95% confidence interval (CI): 0.25–0.67), independent from other possible confounding variables (Maia and de Mendonça, 2002). However, most reviews and epidemiological studies have a weak differentiation between coffee consumption and caffeine intake, with the former containing other bioactive substances, including caffeic acid (Ritchie et al., 2007; van Gelder et al., 2007; Eskelinen et al., 2009; Eskelinen and Kivipelto, 2010; Santos et al., 2010a), chlorogenic acids, and trigonelline, that might also exert potential neuroprotective effects against AD (Socała et al., 2020). It is hard yet essential to evaluate the roles of caffeine separated from other biocomponents in coffee or caffeinated beverages to generate bias minimized findings.

In our recently published systematic review, we conducted a literature search from the Web of Science and PubMed collections covering articles published before February 2022 using the title searching terms, including caffeine, coffee, Alzheimer's disease, and cognition. We did not use the search term tea because these studies often examined the neuroprotective effects of herbal tea rather than those of caffeine. We aimed to elucidate the effects of caffeine on cognition and AD by systematically reviewing all published research relevant to this field. A total of 30 clinical trials have been identified, with 20 out of 30 reporting that caffeine/coffee has a positive effect on cognition and/or decreases the incidence of dementia and AD (Ritchie et al., 2007; Eskelinen et al., 2009; Ritchie et al., 2010; Santos et al., 2010b; Arab et al., 2011; Cao et al., 2012; Vercambre et al., 2013; Al-khateeb et al., 2014; Haller et al., 2014, 2017, 2018; Solfrizzi et al., 2015; Driscoll et al., 2016; Paganini-Hill et al., 2016; Sugiyama et al., 2016; Kim et al., 2019; West et al., 2019; Dong et al., 2020; Iranpour et al., 2020; Lin et al., 2021), and the remaining 10 studies reported no effects (Kyle et al., 2010; Gelber et al., 2011; Hosking et al., 2014; Mirza et al., 2014; Ritchie et al., 2014; Kim et al., 2015; Araújo et al., 2016; Fischer et al., 2018; Cornelis et al., 2020a, b). While most studies are in a line with the hypothesis that caffeine can prevent the progression of AD and especially improve cognitive symptoms, further well-designed studies with large cohorts of participants are warranted to strengthen the evidence and identify the best treatment protocol and mechanistic pathways mediating these effects.

The focus of this mini-review is to give a short overview of the effect of caffeine/coffee on cognition and AD by focusing on the supporting evidence from clinical trials and highlighting the challenges of data interpretation.

Longitudinal Epidemiological Studies

Several studies reported links between caffeine intake and dementia incidence. In the largest study, 13,137 cognitively healthy participants were included (> 65 years) from the project of Kuriyama et al. (2010). This study reported that the incidence of dementia for those who never consumed coffee, or on occasion did or consumed 1–2 cups/d, or ≥ 3 cups/d had a hazard ratio (HR) of 1.00, 0.73 (95% CI: 0.62–0.82), 0.72 (95% CI: 0.61–0.84) and 0.82 (95% CI: 0.65–1.02), respectively. The study also demonstrated that 1–2 cups and ≥ 3 cups of coffee consumption a day were moderately neuroprotective and reduced dementia incidence by 28% and 18% respectively (Sugiyama et al., 2016). Importantly, among non-smokers and non-drinker women, the protective effect of caffeine was more prominent, highlighting the importance of other lifestyle factors on dementia incidence (Sugiyama et al., 2016). While every study has limitations, as the largest published study, the positive outcomes reported here hold the best and highest evidence in the hierarchy of published research to be used to draw conclusions about the effect of caffeine intake on dementia incidence.

Another large-scale study exploring the link between caffeine intake and dementia was reported by Driscoll et al. (2016). 6467 participants were examined from the Women Health Initiative Hormonal therapy randomized controlled trial. The risk of mild cognitive impairment (MCI) was determined by proportional hazard regression based on the baseline caffeine consumption. The study reported that women above the median level of caffeine consumption (261 mg/d mean intake) had only a 26% lower risk of developing dementia or any cognitive impairment (adjusted HR: 0.74, 95% CI: 0.60–0.91) compared to those with below median level intake (64 mg/d mean intake) (Driscoll et al., 2016). However, it is worth mentioning that this study examined only older post-menopausal women.

Another study examining 4809 individuals (> 65 years) focused on cardiovascular health (Arab et al., 2011). While no effect was found for men, in some women the study reported that coffee and tea intake slightly reduced cognitive deterioration rates with no dose-effect association among these women. However, the food frequency questionnaire (FFQ) did not specify the amount of beverage consumed and the caffeine content, only the frequency of consumption which questions the dose-response observations (Arab et al., 2011).

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There is one study that also found no connection between cognitive decline and caffeine consumption in men while coffee intake in women is linked with better cognitive outcomes, with 4197 women and 2820 men were recruited (Ritchie et al., 2007). The study reported that women with higher caffeine intake (> 3 cups/d) exhibited less deterioration in verbal retrieval (OR: 0.67, 95% CI: 0.53–0.85) and visuospatial memory (OR: 0.82, 95% CI: 0.65–1.03) over 4 years than women consuming 1 cup/d or < 1 cup/d. They also reported an age-by-caffeine intake interaction effect on verbal performance during follow-up, with the protective effect being higher for the oldest ≥ 80 years (OR: 0.3, 95% CI: 0.14–0.63) than for 65–74 years women (OR: 0.73, 95% CI: 0.53–1.02). This suggested that in women the effect of caffeine on cognition was confounded by age, but no effect was observed in men (Ritchie et al., 2007).

These findings are also supported by Gelber et al. (2011), who examined 3734 Japanese-American men and found no association between coffee consumption in midlife and the risk of developing cognitive impairment. However, participants with the highest coffee consumption (≥ 411.10 mg/d) were less likely to present brain lesions in 418 decedents (AD, neocortical Lewy bodies, microvascular ischemic lesions, hippocampal sclerosis, and generalized brain atrophy) (OR: 0.45, 95% CI: 0.23–0.89, $P_{trend} = 0.04$) than the group of lowest coffee consumers (≤ 137.0 mg/d) (Gelber et al., 2011).

4368 participants were examined from the Rotterdam study by Mirza et al. (2014). During the short follow-up (0–4 years), high coffee consumers (> 3 cups/d) had a 30% lower risk of developing dementia (HR: 0.70, 95% CI: 0.51–0.96) compared with low consumers (< 1 cup/d). However, this connection was not found after a long follow-up (> 4 years till 21 years) (Mirza et al., 2014).

In line with these results, Araújo et al. (2016) did not find positive effects of coffee consumption on cognition at a longer follow-up. They recruited 2914 participants (59 ± 7.2 years) and reported baseline caffeine consumption was linked with a small decrease in the prevalence of lacunar infarcts (OR per cup: 0.88, 95% CI: 0.79–0.98), smaller hippocampus volume (difference in hippocampal volume per cup increase in coffee consumption = –0.01, 95% CI: –0.02–0.00), a slight enhancement in cognition as demonstrated by the Letter digit substitution task (difference = 1.13, 95% CI: 0.39–1.88), Word fluency test (difference = 0.74, 95% CI = 0.04–1.45), Stroop interference subtask (difference between 0–1 and > 3 cups/d: 1.82, 95% CI: 0.23–3.41), and worsening of cognitive performance in 15-word learning task (difference between 0–1 and > 3 cups/d: –0.38, 95% CI: 0.74–0.02). Importantly, this slight decrease in risk most likely does not lead to observable changes by the person and after 5 years no association was found between higher caffeine intake and improved cognition. The data suggested that caffeine might be a short-term neurostimulator with beneficial effects dimishing after prolonged exposure. However, this link between coffee consumption and cognition was not observed longitudinally (Araújo et al., 2016). These data and the study by Mirza et al. (2014) suggest that a long-term follow-up is important to draw strong conclusions regarding the effects of coffee intake on cognition and dementia risk.

Vercambre et al. (2013) examined 2475 women (≥ 65 years) from the Women's Antioxidant Cardiovascular Study cohort and concluded that caffeinated coffee intake was associated with slower rates of cognitive deterioration ($P = 0.05$) but this link was not found for other caffeinated beverages.

There are several smaller studies that also reported positive effects of coffee consumption on cognition and development of dementia. Solfrizzi et al. (2015) examined 1445 cognitively healthy participants and found that moderate coffee drinkers (1–2 cups/d; HR: 0.31, 95% CI: 0.13–0.75) had a slightly lower incidence of MCI than rare coffee drinkers (< 1 cup/d; HR: 0.47, 95% CI: 0.211–1.02). Interestingly, an increased risk of MCI was reported for those participants with altered coffee intake compared with the constant coffee consumer group (increased by > 1 cup (HR: 1.8, 95% CI: 1.11–2.92), decreased by < 1 cup (HR: 2.17, 95% CI: 1.16–4.08)) indicating an almost doubled risk with alteration in coffee consumption habit. Also, high coffee consumption > 2 cup/d did not correlate with MCI incidence in comparison to rare coffee consumers (HR: 0.26, 95% CI: 0.03–2.11) (Solfrizzi et al., 2015).

Another study recruited 1409 individuals from the Finnish Multinational Monitoring of Trends and Determinants of Cardiovascular Disease (FINMONICA) study (1972, 1977, 1982, 1987). The findings of this study suggested that coffee consumers in midlife had markedly lower dementia and AD risk (Eskelinen et al., 2009). Chronic coffee consumers (3–5 cups/d) at midlife had the lowest risk of dementia (OR: 0.34, 95% CI: 0.16–0.73) and AD (OR: 0.38, 95% CI: 0.17–0.89), indicating a 66% and 62% risk reduction, respectively (Eskelinen et al., 2009).

Santos et al. (2010b) examined 648 individuals (≥ 65 years) and found that women only with 3rd quartile of caffeine intake (> 62 mg/d) had a 51% lower risk of cognitive decline (relative risk: 0.49, 95% CI: 0.24–0.97) compared to participants with 1st quartile of caffeine consumption (< 22 mg/d).

West et al. (2019) examined 638 elderly (≥ 65 years) individuals with type 2 diabetes from the Israel Diabetes and Cognitive Decline study. A subgroup of randomly selected participants ($n = 185$) was examined by magnetic resonance imaging (MRI) to determine white matter (WM) and grey matter volumes. The study reported that higher caffeine consumption was associated with better overall cognition ($P = 0.018$), working ($P = 0.002$) and semantic memory ($P = 0.026$), and executive function ($P = 0.047$) with a more pronounced effect in the older group compared with the younger. In addition, higher caffeine consumption was associated with higher grey matter volume (interaction coefficient $\beta = 0.198$, $P = 0.033$), probably indicating reduced neuronal death in this unique population (West et al., 2019).

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Paganini-Hill et al. (2016) examined an older cohort involving 587 cognitively healthy participants (> 90 years old, mean age = 93 years). The main outcome of this study is that participants consuming > 200 mg/d of caffeine had a 34% lower risk (HR: 0.66, $P < 0.05$) of dementia compared with low caffeine consumers with < 50 mg/d caffeine intake (Paganini-Hill et al., 2016).

One of the few studies that measured plasma caffeine concentration of the study participants was performed by Cao et al. (2012). Two cohorts of 124 participants (65–88 years old) were recruited and plasma caffeine concentration measured at baseline. This study reported that those who showed cognitive decline from initial MCI to dementia had a 51% lower plasma caffeine concentration than participants who maintained the level of cognitive impairment (stable MCI). Importantly, none of the participants with > 1200 ng/mL plasma caffeine concentration progressed to dementia, and 50% of stable MCI participants had higher plasma concentrations than this critical value (Cao et al., 2012). A peak of 10–20 μM plasma caffeine can normally be measured after coffee ingestion and the critical plasma concentration (1200 ng/mL or 6 μM) a few hours after consuming 1–2 cups of coffee (Fredholm et al., 1999; Culmer-Merdek et al., 2005).

Some studies have suggested that caffeine/coffee is a cognitive normalizer instead of a cognitive enhancer. Haller et al. (2017) recruited chronic coffee consumers (1–3 cups/d), including 45 elderly controls and 18 participants with MCI. Participants were grouped into stable-controls cognitive (n = 24), deteriorating-control (n = 21), and MCI (n = 18) groups. The participants were deprived from caffeine for 18 hours and then administered 200 mg caffeine or a placebo 30 minutes before n-back task, a working memory task in functional MRI test. There was no difference in working memory performance between stable-controls cognitive and deteriorating-controls, while in MCI group memory maintenance and recall was less accurate and slower than stable-controls and deteriorating-controls (accuracy 0-back: MCI *vs.* stable-controls: $t_{(40)} = 2.61$, $P = 0.013$, MCI *vs.* deteriorating-controls: $t_{(37)} = 2.72$, $P = 0.010$; accuracy 2-back: MCI *vs.* stable-controls: $t_{(40)} = 3.57$, $P = 0.001$, MCI *vs.* deteriorating-controls: $t_{(37)} = 2.98$, $P = 0.006$; speed slower to 0-back: MCI *vs.* stable-controls: $t_{(40)} = 2.65$, $P = 0.011$, MCI *vs.* deteriorating-controls: $t_{(37)} = 2.26$, $P = 0.030$) assessed by functional MRI n-back tasks (Haller et al., 2017). The deteriorating-control group also had a lower acute caffeine-induced brain activation specific for the right hemisphere ($P < 0.05$) and reduced caffeine-induced default mode network deactivation compared to stable-controls cognitive group ($P < 0.01$). This reduced sensitivity to caffeine in deteriorating-control individuals is in line with the hypothesis that caffeine is a cognitive normalizer and not a cognitive enhancer (Haller et al., 2017). Haller et al. (2018) performed another experiment with 145 cognitively stable elders. After 3 years, an MRI and two neuropsychological assessments were performed, and the participants were then allocated into stable-cognitive (n = 52), intermediate-cognitive (n = 61) and deteriorating-cognitive (n = 32) groups. Moderate coffee consumers were less likely to belong to the deteriorating-cognitive group ($OR_{adjusted}$: 0.447, 95% CI: 0.210–0.952, $P = 0.037$). There was also a negative correlation between voxel-based morphometry and caffeine only for stable-cognitive group, specifically in the left parietal and right frontal WM, suggesting caffeine-induced reduced WM lesions and increased cerebral blood flow in moderate to heavy caffeine consumers when compared to intermediate-cognitive and deteriorating-cognitive groups (Haller et al., 2018). The fact that a positive link between cognition and caffeine intake was only observed in stable-cognitive group strengthens the view that caffeine is a cognitive normalizer instead of a cognitive enhancer.

Fischer et al. (2018) examined 2622 (≥ 75 years) participants from the German study on Aging, Cognition, and Dementia (AgeCoDE). Considering gender and APOEε4 status a multivariate-adjusted joint modeling was applied. This study did not report any significant link between coffee intake and the incidence of dementia or AD (Fischer et al., 2018). However, as discussed above most longitudinal studies and particularly the larger cohort studies seem to show a clear positive effect of caffeine intake on cognition and dementia/AD incidence.

Cross-sectional Studies

A limited number of cross-sectional studies examined the association between coffee consumption, cognition, brain structure and AD pathology such as levels. Cornelis et al. (2020b) performed the largest cross-sectional study by recruiting 445,786 participants (37–73 years) from UK. Coffee intake of ≥ 1 cup significantly decreased reaction time, pairs matching, Trail making test B, and symbol digit substitution. No association was found between cognitive function and caffeine metabolism score × tea, caffeine metabolism score × coffee, and caffeine metabolism score × caffeine (Cornelis et al., 2020b). In another large cross-sectional study, Cornelis et al. (2020a) examined 434,900 participants (37–73 years). The study found that recent coffee consumption was correlated with higher reaction time performance but worse fluid intelligence, pairs matching, and prospective memory for the white participant group only ($P \leq 0.004$). Among non-white participants, similar links were reported for fluid intelligence ($P = 0.09$), pairs matching ($P = 0.03$), and prospective memory ($P = 0.34$) (Cornelis et al., 2020a).

A smaller study by Dong et al. (2020) examined 2513 participants (≥ 60 years) from the National Health and Nutrition Survey. The study found that those with 226.4–495 g/d caffeine intake had a 44% better performance (OR: 0.56, 95% CI: 0.35–0.89) on digit symbol substitution tests (DSST) compared to those with no caffeine consumption using binary logistic reasoning and restricted cubic spline models. Participants with ≥ 384.8 g/d caffeine intake also had moderately better performance on Consortium to Establish a Registry for Alzheimer's

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Disease (CERAD) (OR: 0.68, 95% CI: 0.48–0.97) compared with the lowest quartile caffeine consumers (OR: 0.62, 95% CI: 0.38–0.98). A positive relationship was found between caffeine/coffee intake and CERAD and DSST score and no link between decaffeinated coffee intake and cognition (Dong et al., 2020).

Iranpour et al. (2020) examined 1440 adults (> 60 years) from the National Health and Nutrition Examination Survey. Better cognitive function was positively associated with the highest quartile of caffeine consumption in the crude model ($P < 0.05$). After adjusting for confounding factors, this link was only marginally significant in the CERAD word recall test ($P = 0.09$), and this trend was more pronounced among men (B = 0.001, $P = 0.004$) but not in women (B = 0.00007, $P = 0.89$) (Iranpour et al., 2020). This is in contrast to the other findings (Ritchie et al., 2007; Ritchie et al., 2010) reporting that the beneficial effect of caffeine on cognition was enhanced among women and not men.

A brain MRI study by Ritchie et al. (2010) examined 641 elderly participants (> 65 years). The study reported that women with more than three units of caffeine intake had a significantly lower mean log transformed WM lesions/cranial volume ratio (–1.23 ± 0.06) than women who consumed 2–3 units (–1.04 ± 0.04) or 1 unit or less (–1.04 ± 0.07) of caffeine. In addition, chronic coffee consumers had increased cerebral perfusion, suggesting that coffee might be neuroprotective. However, this association was only observed among women (Ritchie et al., 2010).

In a small study, Kyle et al. (2010) recruited 351 participants (64 years) and assessed them on a Moray house test and MONItor trends in Cardiovascular diseases (MONICA) FFQ. Caffeine consumption was correlated with a slower digit symbol ($F = 3.38$, $P < 0.02$), but after accounting for socioeconomic status (SES) this correlation was not observed. There was no evidence to indicate that caffeine had any effect on cognition (Kyle et al., 2010).

Aβ load and its link with caffeine intake were examined in two studies. Ritchie et al. (2014) assessed 1193 elderly (≥ 65 years), including those with depressive symptomology and type 2 diabetes. Higher caffeine intake was associated with a decrease in incidental diabetes in men (HR: 0.64, 95% CI: 0.42–0.97) and a significant increase in incidental diabetes risk in women (HR: 1.51, 95% CI: 1.08–2.1), but no relationship was observed between caffeine and depression or levels. The study also reports that caffeine was not neuroprotective against dementia among women and decreased risk of dementia among heavy caffeine-consuming women was not confounded by diabetes or depression (Ritchie et al., 2014). Another study recruited 411 participants and allocated them into cognitive normal ($n = 282$) and MCI ($n = 129$) groups after screening (Kim et al., 2019). Based on current and lifetime coffee intake participants were classified into low coffee intake (< 2 cups/d) and high coffee intake (≥ 2 cups/d) categories. Positron emission tomography and MRI were utilized to measure cerebral Aβ deposition, AD signature region cerebral glucose metabolism, AD signature region cortical thickness, and WM hyperintensities. While higher coffee consumption was associated with a lower Aβ load, low coffee intake was not even after adjusting for confounding factors. However, coffee consumption habit was not linked with hypometabolism, AD-signature region, and WM hyperintensities volume (Kim et al., 2019). This finding was in contrast to MRI studies by Ritchie et al. (2010) and Haller et al. (2018) who found caffeine decreased the amount of WM lesion/cranial volume in cognitively stable elderly.

These cross-sectional studies are more prone to reverse causality and cannot confirm causality, but the data reveal some useful details about the action of caffeine on cognition and AD-related pathology.

Randomized Control Trials

Only two small cross-sectional studies examined the link among coffee intake, cognition, and brain structure. Haller et al. (2014) conducted a double-blind placebo-controlled functional MRI study during an n-back working memory test in MCI ($n = 17$, 70.7 ± 4.6 years) and healthy controls ($n = 17$, 68.3 ± 2.8 years). Participants were chronic coffee consumers (1–3 cups/d) but they did not consume caffeine for 18 hours and were given 200 mg of caffeine or placebo tablets 30 minutes prior neuroimaging. Acute caffeine intake resulted in higher prefrontal activation in healthy individuals and less localized posteromedial activation in participants with MCI. In MCI, tensorial-independent component analysis found caffeine-induced increases in the activation of prefrontal cortical areas, supplementary motor areas, ventral premotor, parietal cortex, basal ganglia, and cerebellum in comparison to healthy individuals. These findings might indicate that caffeine-induced posterior shift of working memory-related brain activation patterns in MCI could counterbalance frontal lobe dysfunction (Haller et al., 2014). Therefore, this study also supports the notion that caffeine acts as a cognitive normalizer and not an enhancer, in agreement with the longitudinal epidemiological studies (Haller et al., 2017, 2018).

A similar study by Lin et al. (2021) examined 20 healthy young (18–35 years) habitual coffee drinker male subjects with good sleep patterns, 18–25 kg/m^2 BMI and no substance use. During a 9-day ambulatory phase, 10 individuals were placed on (3 × 150 mg/d) caffeine and the other 10 were given a placebo (3 × 150 mg/d mannitol). The study found that higher caffeine consumption was linked with decreased grey matter volume in the medial temporal lobe compared with placebo group, even after adjusting for increased cerebral blood flow triggered by caffeine. Sleep quality was not affected but caffeine intake was linked with poor working memory. However, the main limitations of the study were the small sample size and inclusion of males only. In addition, due to the young age of the participants, the data might have even more limited generalizability, especially when predicting outcomes in the elderly (Lin et al., 2021).

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Discussion

The failure of AD drug clinical trials is shifting the focus of researchers to dietary interventions or nutraceuticals that could potentially delay AD onset or progression. Caffeine and its sources, such as coffee and tea, are gaining increasing interest in this field because of their promising beneficial effects against cognitive deficits, and possibly AD (Fredholm et al., 1999; Maia and de Mendonça, 2002; Schreiner and Popescu, 2022). The clinical trials reviewed here provide some evidence that coffee consumption is protective against cognitive decline and possibly AD (**Figure 1** and **Additional Table 1**), but further clinical trials are needed to strengthen and prove this association. 18 out of the 29 studies that have been included in the current review reach a consensus on the beneficial effects of caffeine (Ritchie et al., 2007; Eskelinen et al., 2009; Ritchie et al., 2010; Santos et al., 2010b; Arab et al., 2011; Cao et al., 2012; Vercambre et al., 2013; Driscoll et al., 2016; Paganini-Hill et al., 2016; Sugiyama et al., 2016; Haller et al., 2017, 2018; Kim et al., 2019; West et al., 2019; Dong et al., 2020; Iranpour et al., 2020; Lin et al., 2021). It must be emphasized that most of these studies employed questionnaires, self-reported 24 hours dietary recall, or interviews to record the number of cups of coffee or caffeinated beverages consumed. Therefore, the daily intake of caffeine was estimated. These methods inevitably induce recall bias from incomplete or inaccurate recollection of information and misclassification bias from selection of caffeine intake categories by participants, both of which would influence the association between caffeine intake and its effect (Leviton, 2018). Additionally, the beneficial effects against cognitive decline might not be solely dependent on, but at least partially achieved by, caffeine, due to the existence of other bioactive constituents in coffee. Many studies support the notion that coffee is one of the best sources of neuroprotective antioxidants available (Yashin et al., 2013; Ikram et al., 2020; Socała et al., 2020), and coffee consumption is also linked with lower risk of total and cause-specific mortality (Freedman et al., 2012; Poole et al., 2017; Loftfield et al., 2018). Caffeine-only neuroprotection has also been testified in animal studies (Paiva et al., 2022). Moreover, although many studies included in this review have relatively large sample sizes and long follow-ups, the heterogeneity between studies regarding study designs, study populations, measurements of caffeine intake and cognitive status might lead to different conclusions. Some important confounding factors, such as diet, physical activities, cultural differences, and lifestyle-related diseases (diabetes mellitus and hypertension), that are impossible to be excluded also have significant impacts on the results. Hence, further large cohort studies with rigorous designs are needed to validate the findings.

Only one study from Cao et al. (2012) examined plasma caffeine concentration among 124 participants longitudinally and reported that cognitive decline during 2 to 4 years follow-up was accompanied with significantly lower baseline plasma caffeine concentration than those who maintained their cognitive performance (i.e., stable MCI). The measurement of plasma caffeine concentration is more objective than using recall questionnaires or interviews for caffeine intake estimation. But there are also some apparent drawbacks of this study, including small sample size, short follow-up, only one point of plasma caffeine concentration measurement, as well as failure of accounting for other significant confounding factors (i.e., lifestyle) (Cao et al., 2012). The pharmacokinetics of caffeine is vital when considering its potential neuroprotective effects.

Future epidemiological studies with plasma caffeine concentration data and surveys recording extensive data on confounding variables, including data on cytochrome (*CYP*) genotype are urgently needed. Caffeine is metabolized for clearance in humans mainly through the N-3-demethylation to paraxanthine pathway by *CYP1A2* in the liver (Begas et al., 2007). Genetic variance of the *CYP1A2* gene causes variability in caffeine metabolism and plasma caffeine concentration between individuals and can cause variation in physiological effects (Thorn et al., 2012). Smokers have accelerated caffeine metabolism resulting in a lower plasma caffeine concentration (Pollock et al., 1999). Furthermore, exogenous estrogens can also inhibit caffeine metabolism and induce increased plasma caffeine concentration (Pollock et al., 1999). The sex-dependent effect of caffeine on cognition also deserves more in-depth investigations in future studies, given the contradictory conclusions from studies (Ritchie et al., 2010; Iranpour et al., 2020), which claimed stronger benefits for either men or women.

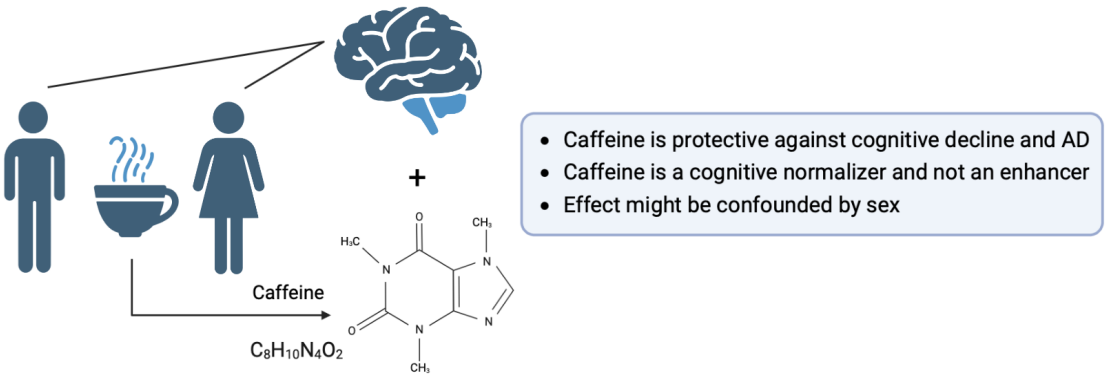

Figure 1: Caffeine positively effects cognition and might prevent or slow down the progression of Alzheimer's disease (AD).
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Only one study highlighted the potential negative effect of caffeine, which found cognitively healthy individuals who changed their habitual coffee intake pattern by increasing their amount of coffee consumption (> 1 cup/d) over 3.5-year follow-up had a higher chance of MCI incidence than those with reduced coffee drinking habits (< 1 cup/d) (HR: 2.17, 95% CI: 1.16 – 4.08) or with those who maintained their habits in coffee consumption (± 1 cup/d) (HR: 1.80, 95% CI: 1.11 – 2.92) (Solfrizzi et al., 2015). Albeit this potential negative effect of coffee consumption alterations discovered, the study also proposed habitual moderate amount of coffee (1 – 2 cups/d) is associated with significantly lower rate of the MCI incidence than those who never or rarely consumed coffee. This is of great practical importance as the caffeine habit is highly likely to change over the lifespan for most individuals, which might be detrimental to cognition maintenance according to these findings. However, this study used FFQ to estimate coffee consumption and did not adjust for unmeasured confounding variables (i.e., lifestyle or social status), both of which might contribute to cognitive decline. Importantly, the relatively short follow-up prevents generalization of findings beyond the examined age group. Hence, in future studies, caffeine intake data should be collected at multiple time points including midlife and during longer follow-up to examine alterations in behavior, cognition, brain structure and function. Cognition should also be assessed by verified methods, i.e., mini-mental state examination (MMSE), clinical dementia rating, CERAD and a sub-group subjected to brain imaging to identify changes in neural architecture, and lesions and examine cerebral perfusion. Ideally, this subgroup has to undergo post-mortem examination to determine the presence and stage of AD. Haller et al. (2014, 2017) found an increase in compensatory basal activity diffused through the posto-temporal region of the brain in early cognitive decline, which increases the brain's sensitivity to the neuroprotective action of caffeine. In addition, MRI studies by Ritchie et al. (2010) and Haller et al. (2018) demonstrated that caffeine reduces the amount of WM lesion/cranial volume in cognitively stable elders. In agreement with this, Gelber et al. (2011) reported high caffeine intake was associated with a lower occurrence of any brain lesion types at autopsy. Ritchie et al. (2014) found increased cerebral perfusion in chronic coffee consumers, indicating a possible neuroprotective mechanism of coffee. However, Kim et al. (2019) did not report any association between coffee habit and hypometabolism, atrophy of AD signature, and WM hyperintensities volume; however, this study found that coffee has a neuroprotective effect by reducing Aβ levels as measured using a three-dimensional ^{11}C Pittsburg compound B-positron emission tomography.

Besides the most common symptoms of memory loss and cognitive decline, several behavioral and psychiatric symptoms, such as anxiety, stress, and depression are associated with AD or dementia, adding extra burden for patients and their caregivers (Mayeux, 2010). Digging into the possible reasons behind the adverse sides of coffee consumption, the first might be caffeine's potential link with the already elevated stress levels and anxiety, both of which are independent predictive markers of increased chance of later conversion to AD among MCI patients (Teri et al., 1999; Lyketsos et al., 2000; Porter et al., 2003; Craig et al., 2005; Palmer et al., 2007; Kaiser et al., 2014). Secondly, a meta-analysis regarding the association of blood pressure (BP) and coffee intake among non-hypertensive healthy participants suggested a small increase in both systolic and diastolic BP associated with regular caffeine or coffee intake (Noordzij et al., 2005; Zhang et al., 2011). The elevated BP, or at least the BP variability (BPV), induced by coffee intake might exert detrimental effects on AD progression. One piece of evidence comes from the Lattanzi et al. (2014) that examined the MMSE score and BPV of 240 mild to moderate probable AD patients for a 12-month period and showed patients characterized by faster cognitive deterioration had significantly greater systolic BPV in comparison to patients with slower cognitive decline. Another cohort study by Alperovitch et al. (2014) investigated BPV and dementia incidence of 6506 elderly individuals. After 8 years of follow-up, the BPV rather than mean BP was associated with an increased risk of dementia. The coffee-induced BPV might alter cerebral hemodynamics and favour the deterioration of cognitive deficits among those early AD subjects with compromised cerebral autoregulation (Román and Kalaria, 2006; Lattanzi et al., 2014). It is noteworthy that one study scrutinized caffeinated/decaffeinated coffee and intravenous caffeine (250 mg) or placebo (normal saline) administration among 15 healthy volunteers (6 habitual and 9 non-habitual coffee drinkers) and proposed that ingredients other than caffeine increased BP (Corti et al., 2002). As said, not only careful interpretation of current literature using coffee as caffeine estimation is vital, but also there is an urgent need to develop future AD-focus studies with better differentiation between the effect of caffeine and coffee. Last but not least, sleep disturbances and insomnia are more prevalent among the elderly and MCI/AD patients (Sadeghmousavi et al., 2020). It is not surprising that coffee intake is dose-dependently associated with vigilance and sleepiness reduction (Clark and Landolt, 2017). A study from Osorio et al. (2011) assessed the relationship between insomnia and AD in 346 cognitively healthy older subjects (75.9 ± 6.6 years old) over 7.7-year follow-up showed a faster progression to dementia among baseline normal and later AD patients with insomnia. The complex negative interplay between insomnia or sleep disturbance and AD development presses the need to further explore caffeine-related sleep alternations and caffeine's potential negative effects regarding AD. From the mechanistic point of view underlying AD predisposition, many studies proposed the consequential outcomes of sleep impairments which might be linked to coffee intake, including but not limited to extracellular tau release and Aβ aggregation (Pooler et al., 2013; Di Meco et al., 2014; Chen et al., 2017), inflammation and elevated levels of proinflammatory cytokines (Irwin, 2015; Irwin et al., 2016),

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blood-brain barrier disruption (He et al., 2014), and reduction in neurotrophin levels (Faraguna et al., 2008). In addition, a functional MRI study involving 30 participants with primary insomnia found that these subjects exhibited abnormalities in the neuronal network connectivity associated with spatial working memory compared to healthy controls (Li et al., 2016).

A few *in vivo* and *in vitro* studies highlighted the effect of caffeine on amyloid precursor protein processing, by shifting it to a non-amyloid pathway leading to reduce Aβ load and cognitive decline (Arendash et al., 2006, 2009; Cao et al., 2009; Janitschke et al., 2019). In addition, caffeine promotes neuroprotection by reducing the aggregation (Laurent et al., 2014; Mancini et al., 2018) and increasing the clearance of Aβ (Qosa et al., 2012). There is also evidence that caffeine can exert a neuroprotective effect via its actions as a non-selective adenosine receptor antagonist (Dall'Igna et al., 2007; Espinosa et al., 2013; Bortolotto et al., 2015; Li et al., 2015; Zhao et al., 2017). Caffeine is shown to reduce acetylcholinesterase activity (Mohamed et al., 2013; Pohanka and Dobes, 2013) and brain-derived neurotrophic factor levels (Han et al., 2013; Moy and McNay, 2013). Additionally, caffeine affects membrane properties (Gastaldo et al., 2020), changes excitatory and inhibitory neurotransmission (Zappettini et al., 2019), reduces endolysosomes dysfunction (Soliman et al., 2017), and increases granulocyte-colony stimulating factor levels (Cao et al., 2011). These mechanisms are proposed to be involved in neuroprotective effects of caffeine against AD.

A few clinical observations have also suggested that caffeine/coffee is not a cognitive enhancer but rather a cognitive normalizer (**Figure 1**). Therefore, healthy adults or those with declining cognition could expect a very little benefit if any from coffee/caffeine consumption (Haller et al., 2014, 2017, 2018; West et al., 2019). Haller et al. (2014) reported no alterations in neural activation suggesting that caffeine is not a cognitive enhancer. Coffee does not have a positive effect on cognitive function in case of severe cognitive decline (Haller et al., 2017, 2018). Also, caffeine decreases the amount of WM lesion/cranial volume and increased cerebral perfusion in cognitively stable elders but has no benefits in participants with cognitive decline (Haller et al., 2018). Another functional MRI study reported that caffeine reduced cognitive decline in deteriorating controls, but neural activation was not seen at the same level as in participants with stable-cognitive performance (Haller et al., 2017).

The current literature is not conclusive regarding the role of sex in caffeine-induced neuroprotection (Ritchie et al., 2007, 2010; Sugiyama et al., 2016; Iranpour et al., 2020) (**Figure 1**). Two studies reported a significant effect of caffeine on cognition for women only in the study population (Ritchie et al., 2007, 2010). In another study, coffee intake reduced dementia incidence and the effect was stronger within the non-smoker and non-drinker female cohort (Sugiyama et al., 2016). Iranpour et al. (2020) found that caffeine has a neuroprotective effect in both sexes, but after adjusting for confounding factors, this effect of caffeine was weak and detected in the male group only. The precise mechanism that might underlie the difference in neuroprotective properties of caffeine/coffee between sexes may be impacted by differences in caffeine metabolism, pharmacodynamics, or hormonal milieu (Ritchie et al., 2010; Iranpour et al., 2020) but these relationships remain to be unravelled. Further research has to be designed to clarify if there are sex differences in the effects induced by caffeine/coffee on brain function, cognition and the progression of AD pathology.

Conclusion

In conclusion, based on theoretical considerations and fundamental research in human subjects, dietary caffeine intake may exert some beneficial effects against dementia and possibly AD and may be a viable therapeutic approach. However, further studies are needed to replicate and strengthen this link by minimizing potential biases and confounding factors that are inherent to all epidemiological studies. Moreover, the optimal dose and frequency of daily caffeine intake also deserves thorough investigation in future studies. As previously mentioned, there are many other substrates within coffee and caffeinated beverages that might also have additional effects. The lack of clinical trials on caffeine makes this topic controversial and inconclusive. It is also imperative to identify the molecular targets and mechanisms of caffeine in the central nervous system that facilitate its neuroprotective effects. These effects need to be explored in both sexes and different age groups, which would greatly help in the development of new therapeutic options. Nevertheless, this review has provided a comprehensive insight into the effects of caffeine/coffee on cognition and AD, shedding more light on the interesting opportunity for new research questions and theories in this field.

Author contributions

All authors contributed to literature search and writing. YZ prepared the figure and table. AK participated in the conceptualization and supervision. All authors read and approved the final version of the manuscript.

Conflicts of interest

No conflict of interest.

Data availability statement

All data relevant to the study are included in the article or uploaded as Additional files.

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Additional file

Additional Table 1: Cinical studies investigating the effects of caffeine on cognitive function in dementia.

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