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Evidence Surrounding the Relation between Coffee and Cognitive Function

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Abstract

The purpose of this narrative review was to discuss the most compelling empirical evidence pertaining to the potential relation between coffee consumption, cognitive function, and Alzheimer's disease (AD). Sixteen studies were identified and selected based on cognitive outcomes (performance, decline, dementia and AD). The majority of retrospective studies suggest a positive association between coffee intake and cognitive performance, implying a possible therapeutic strategy for those affected with AD. Similarly, most prospective cohort studies suggest that coffee consumption is associated with reductions in cognitive decline, and onset of dementia and AD. Unfortunately, few human studies differentiate between the effects of caffeinated vs. decaffeinated coffee. Recent studies in animals suggest that the presumed neuroprotective effect of coffee is not completely accounted for by caffeine, but may be due to a combinatory effect of caffeine with other bioactive compounds in coffee (e.g., eicosanoyl-5-hydroxytryptamide). As such, additional research in humans is warranted, particularly regarding the effects of caffeinated vs. decaffeinated coffee on cognitive function and AD. Despite the lack of evidence of a causal relation, coffee consumption in the morning carries few known risks and may be associated with improvements in cognitive function.

Keywords: Coffee; Caffeine; Caffeinated Coffee; Decaffeinated Coffee; Dementia; Alzheimer's Disease; Cognitive Decline; Cognitive Performance

Introduction

Alzheimer's disease (AD), the most common form of dementia, remains the 6th leading cause of death in the United States [1]. It causes functional problems with thinking, memory and behavior, and can afflict a broad age range in both early-onset and late-onset forms [2]. More than 5 million Americans currently live with the disease, a number expected to increase to as much as 16 million by 2050 [3,4], and the associated costs are estimated to reach $1.2 trillion in 2050 [5]. Current treatments are limited both in availability and efficacy. These include five FDA-approved medications, which are relegated to providing symptomatic control of the disease and may carry side effects [6]. However, because the pathology of the neurodegenerative dementias precedes symptom onset, sometimes by decades [7], interest in developing preventive intervention strategies that target earlier stages of disease has increased.

Although genetics play a key role in the pathogenesis of the disease [8], lifestyle and environmental factors also contribute to the development and progression of AD. In particular, an research in the last decade has suggested that there may be in important connection between nutrition and cognitive function. Studies have shown that particular "brain-healthy" nutritional interventions may help reduce cognitive decline, protect against the onset of AD, and even improve cognitive function in individuals with AD [9]. In fact, several studies of nutritional interventions have shown therapeutic effects as large as those observed with current FDA-approved medications for AD [10,11].

A number of prospective studies have suggested that adherence to a Mediterranean diet has neuroprotective effects [12-14] and may help individuals with AD regain some cognitive function. However, a Mediterranean diet may be costly and difficult to maintain, particularly in the United States. Coffee, on the other hand, is one the most frequently consumed beverages in the world [15] and some recent evidence suggests that this common dietary staple may also be related to cognitive function. This narrative review describes the results of studies designed to examine the potential association between coffee consumption and cognitive function and/or risk of developing AD. We also highlight some of the limitations of the relevant literature, and offer evidence-based recommendations for health care providers and caregivers of individuals already diagnosed with, or concerned about developing, AD.

Materials and Methods

The authors performed an electronic search and identified papers published in English that investigated the relation between coffee and cognition, mild cognitive decline (MCI), dementia and/or AD. The search was conducted between June and July 2014, utilizing articles from PubMed. Search terms included coffee, cognitive, MCI, dementia, and Alzheimer's disease. Twelve epidemiological and four animal studies are discussed. Because our objective was to discuss the evidence surrounding caffeinated or decaffeinated coffee consumption in delaying the onset of AD, reports not including coffee as an independent variable (e.g. studies measuring caffeine intake based only on tea, cola drinks, energy drinks and/or dietary supplements) were excluded.

Results

Currently, there are no randomized controlled trials (RCTs) evaluating the effect of dietary coffee or caffeine on AD.

Coffee and risk of developing Alzheimer's disease and dementia

The Canadian Study of Health and Aging following 4615 subjects aged 65 and older, over a five-year period, assessed coffee consumption using a risk questionnaire [16]. Daily coffee consumption was significantly associated with a 31% reduction in risk of AD (OR = 0.69, 95 % CI: 0.50-0.96). Information about risk factors (e.g. coffee intake) was gathered from a self-administered questionnaire, which covered sociodemographic characteristics, occupational and environmental exposures, lifestyle, family, and medical history. Regular consumption of tea and coffee was defined as nearly every day, but specific amounts (cups or ounces) were not specified. Screenings for dementia involved using the Modified Mini-Mental State (3MS) Exam via a 2 phase-procedure, including an interview and a clinical exam. Over the five-year period, 194 cases of AD were reported and a significant association was found between coffee consumption and a reduced risk of AD. Interestingly, when decedents were excluded from the analysis, the association with coffee consumption remained below 1.0, but was no longer statistically significant (OR = 0.91 95 % CI: 0.73-1.14).

Individuals who participated in the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study showed a 65% decrease in the risk of developing AD and dementia in late-life (age 65-79) as a result of coffee consumption during mid-life [17]. Coffee, categorized intro three groups: 0-2 cups (low), 3-5 cups (moderate) and > 5 cups (high), was assessed as part of a 135-item survey questionnaire in 1409 subjects at midlife. Cognitive status was assessed using a three-step protocol for the diagnosis of dementia (including a MMSE screening, a clinical and a differential dementia and AD diagnostic phase). A total of 61 persons met the diagnosis of dementia, out of which 48 had AD. The lowest risk was found in subjects who drank 3–5 cups/day over a 21-year follow up period. Although the authors did not specify the number of ounces per cup of coffee, nor did they stratify by caffeinated vs. decaffeinated content, a logistic regression model adjusted for possible confounders,

such as midlife age, sex, education, follow-up time, smoking, serum total cholesterol, BMI, and physical activity, revealed that moderate coffee consumption (in comparison to low and high), had the greatest protective effects on dementia (OR = 0.35, 95% CI: 0.16–0.75) and AD (OR = 0.36, 95% CI: 0.15-0.86).

Results, however, are not unequivocal. The Honolulu-Asia Aging Study reported no significant associations between coffee or caffeine intake during midlife and risk of cognitive impairment, overall dementia or AD later in life [18]. Coffee consumption at baseline was derived via self-report in this nested case control study of 3494 men who entered the study during midlife between 1965 and 1968 (mean age 52 years old). Through 2004, 573 individuals were diagnosed with cognitive impairment or dementia. However, neither coffee nor caffeine consumption at baseline was found to predict any cognitive outcome.

Coffee and risk of cognitive decline

In a French population-based cohort of 4197 women and 2820 men aged 65 and older, caffeine intake (as defined by self-reported cups of coffee and tea) was assessed at baseline and at 2- and 4- year follow-up [19] period Questions relating to caffeine consumption were included in a standardized interview administered by either psychologists or research nurses. The principal outcome measure was cognitive decline. The cognitive examination consisted of the MMSE, a test of visuospatial recall, and a test of verbal recall and fluency. Results indicated no relationship between coffee intake and incident dementia from all causes (n = 283, p = 0.76) or AD (n = 184, p = 0.96). However, women with high rates of caffeine consumption (over three cups per day) showed less decline in verbal retrieval (OR = 0.67, 95% CI: 0.53-0.85) over 4 years than women consuming one cup or less per day. When examining coffee consumption separately in women consuming three or more cups, decline on the verbal fluency test was observed (OR = 0.82, 95% CI: 0.66-1.01). This effect was, however, not seen in men.

In a study comparing coffee consumption among a cohort of 676 elderly men from Finland, Italy, and the Netherlands, decline in cognitive performance over 10 years was 4.3 times smaller than the decline of non-consumers [20]. Information on the frequency of cups of coffee consumption was obtained either via a standardized self-administered questionnaire or interview with a dietitian. Global cognitive function was assessed using the MMSE in each survey year. The MMSE scores ranged from 0 to 30— a higher score reflecting better cognitive performance. The results indicated that men who consumed coffee had a 10-year cognitive decline of 1.2 points (4%). Non-consumers had an additional decline of 1.4 points ($p < 0.001$). The least cognitive decline was for three cups of coffee per day (0.6 points), which was 4.3 times smaller than the decline of non-consumers ($p < 0.001$). Although no differentiation was made between the effects of caffeinated and decaffeinated coffee, study findings suggest that consuming coffee reduces cognitive decline in elderly men.

A recent report by Vercambre and colleagues [21] looked at 2475 women aged 65 and older. Regular caffeine intake was measured at baseline (1995–1996) using the Willet Semiquantitative Food Frequency Questionnaire (FFQ), a validated 116 item-FFQ. From 1998–2000 to 2005–2006, four telephone cognitive assessments evaluating global cognition, verbal memory, and category fluency at two-year intervals were conducted. The primary outcome was the change in global cognitive score. Global cognition was evaluated with the Telephone Interview of Cognitive Status, a telephone adaptation of the MMSE (range 0 to 41 points). A significant association between increasing caffeinated coffee consumption and slower cognitive decline was found (the difference in rate for global score change for ≥ 4 cups / day vs. none = 0.02 (95% (CI) = 0.00-0.05), p-trend = 0.05). The potential association with decaffeinated coffee failed to reach significance (the difference in rate for ≥ 2 cups/day vs. none = −0.01 (95% CI = −0.03-0.01), p-trend=0.09).

Hameleers and colleagues [22] examined a group of healthy adults (N = 1875, aged 24 - 81 years). Participants filled a questionnaire at home with respect to sociodemographics, as well as coffee intake, and were invited for neuropsychological testing. Cognitive tests included the Visual Verbal Learning Test, Motor Choice Reaction Test, Letter Digit Substitution Test, Fluency, Concept Shifting Test, and Stroop Color Word Test. Although the authors point out a lack of relation to short-term memory across multiple age groups, higher habitual coffee consumption was found to be associated with better long-term memory [22]. Conversely, van Boxtel and colleagues [23] found no relationship between caffeine consumption and cognitive change over time. Information on the intake of caffeine-containing beverages was available from the same baseline questionnaire used by Hameleers et al [22]. After 6 years, 1376 individuals were available for reassessment, and after correction for demographic characteristics, baseline performance and health status, results indicated that while movement times of the Motor Choice Reaction Test tasks was preserved, verbal memory performance was not [23].

Coffee and cognitive performance

A cross-sectional survey of a representative sample of 9003 British adults aged 18 and older (the Health and Lifestyle Survey) examined the relationship between coffee consumption and cognitive performance [24]. Subjects were asked to complete cognitive tests of simple reaction time, choice reaction time, incidental verbal memory, and visuo-spatial reasoning, in addition to providing self-reports of usual coffee and tea in-

take, in number of cups. A dose-response trend to improved

Table 1. Epidemiological Evidence Surrounding the Relation between Coffee & Cognitive Function[1]

Study	Design	Subjects (Age)	Follow Up Period	Coffee Intake Collection Methods	Cog Function: Assessment Tools	Results	Measure of Significance
Eskelinen et al. (2009)	Prospective, Cohort	N = 1409 (65-79 yrs)	21 yrs	135-item survey, coffee intake: 0-2 cups = low, 3-5 cups = moderate, >5 cups = high	Dementia & AD diagnosis: MMSE[2] screening, clinical & differential evaluations	65% ↓ risk of dementia & AD in late life; greatest protective effect from moderate coffee consumption (3-5 cups/d) during mid-life	AD OR = 0.36, 95% CI = 0.15-0.86; dementia OR = 0.35, 95% CI = 0.15-0.86
Laitala et al. (2009)	Prospective, Cohort	N = 2606 twins (≥65 yrs)	28 yrs	Self-report postal questionnaire	Cog status and risk of MCI & dementia: Telephone interview (TELE) & Telephone Interview for Cog Status (TICS)	Coffee consumption not assoc w/cog performance in old age & did not affect risk of MCI or dementia	NS[3]
Lindsay et al. (2002)	Prospective, Cohort	N = 4615 (≥65 yrs)	5 yrs	Self-administered questionnaire	Screening for dementia & AD: Modified Mini-Mental State (3MS) Examination & clinical exam	31% ↓ in risk of AD	OR = 0.69, 95% CI = 0.50-0.96
Ritchie et al. (2007)	Prospective, Cohort	N = 7027 (≥65 yrs)	4 yrs	Standardized interview administered by psychologists or nurses	Cog decline, incident dementia & AD: MMSE, test of visuospatial recall, & a test of verbal recall & fluency	No relation betw coffee intake & incident dementia or AD; however women taking >3 cups/d showed ↓ decline in verbal retrieval	Verbal retrieval OR = 0.67, 95% CI = 0.53-0.85
van Boxtel et al. (2003)	Prospective, Cohort	N = 1376 (24-81 yrs)	6 yrs	Self report: No or Yes: 1–3, 4–6, 7–10, & 10+ cups/d	Visual Verbal Learning, Motor Choice Reaction, Letter Digit Sub, Fluency, Concept Shifting, & Stroop Test	No relation betw coffee consumption & cog change	NS
van Gelder et al. (2007)	Prospective, Cohort	N = 676 men (74.9-77.4 yrs)	10 yrs	Standardized self-administered questionnaire: coffee consumption categorized into yes/no and into 0-4 and >4 cups/d	Global cog function and decline: MMSE	Men who did vs. did not consume coffee had 10-yr cog decline of 1.2 vs. 2.6 points. Least cog decline for 3 cups/d	$p < 0.001$
Vercambre et al. (2013)	Prospective, Cohort	N = 2475 women (≥65 yrs)	5 yrs	116-item Willet Semi-quantitative FFQ[4]	Global cognition and decline, verbal memory, & category fluency: Telephone Interview of Cog Status	Significant relation betw increasing caffeinated coffee (≥4 cups/d) & slower cog decline	$p = 0.05$
Corley et al. (2010)	Retrospective, Cohort	N = 923 (70 yrs)	N/A[5]	Scottish Collaborative Group 165-item FFQ v7.0	Cog performance: MMSE, specific subtests from WAIS-III, WMS-III, and Verbal Fluency (NART & WTAR)	Drinking ground coffee assoc w/performance on Nat Adult Reading Test & Wechsler Test of Adult Reading	NART $p = 0.007$ WTAR $p = 0.02$
Gelber et al. (2011)	Retrospective, Nested Case Control	N = 3494 men (mean 52 yrs)	25 yrs	Standardized, validated 24-hour dietary recall	100-point CASI (a combination of Hasegawa Dementia Screening Scale, Folstein MMSE, & Modified Mini Mental State Test)	No relation betw coffee intake during midlife & risk of cog impairment, overall dementia or AD	NS
Hameleers et al. (2000)	Cross-sectional	N = 1875 (24-81 yrs)	N/A	Questionnaire. Ss indicated: 0-2, 3-5, 6-9, or 9+ cups coffee/day	Visual Verbal Learning, Motor Choice Reaction, Letter Digit Sub, Fluency, Concept Shifting, & Stroop Test	↑ coffee consumption assoc w/ better long term memory	$p < 0.05$
Jarvis et al. (1993)	Cross-sectional	N = 9003 (≥18 yrs)	N/A	Self-reports of usual coffee & tea intake, measured in cups/d: (none, 1 or 2, 3 or 4, 5 or 6, 6+)	Cog performance: Simple reaction time, choice reaction time, incidental verbal memory, & visuo-spatial reasoning	Dose-response trend to ↑ performance w/ ↑ levels of coffee consumption on all 4 tests	$p < 0.001$
Johnson-Kozlow et al. (2010)	Cross-sectional	N = 1528 (mean 72.6 yrs)	N/A	Willet Semi-quantitative FFQ containing two items assessing caffeinated and decaffeinated coffee intake during past yr	Cog function: 12 standardized tests, including MMSE	↑ lifetime coffee consumption in women assoc w/ ↑ performance on 6 of 12 tests Current caffeinated coffee intake assoc w/ ↑ performance on 2 of 12 tests	$p \leq 0.05$ $p < 0.05$

[1] Articles reported in order of rigor of methodological design: Prospective, followed by Retrospective, and Cross-sectional studies
[2] MMSE = Mini Mental State Examination
[3] NS = Non-significant
[4] FFQ = Food Frequency Questionnaire
[5] N/A = Not Applicable

Table 2. Animal Evidence Surrounding Relation between Coffee & Cognitive Function

Study	Design	Sample Size	Follow Up Period	Coffee-related intervention	Cog Function Testing	Results	Measure of Significance
Arendash et al. (2010)	Experiment	N = 57 Aβ PPsw+PS1[1] double transgenic mice (Tg) (4-9 mo old)	6 mo	~1 mg/d of theophylline, a major component of caffeine, administered in drinking water, beginning at 5.5 months of age	6-wk battery of sensorimotor, anxiety, & cog-based tasks, testing spatial learning / memory, identification / strategy switching, & working memory	No effects of theophylline	NS
Basurto-Islas et al. (2014)	Experiment	N = 60 30 female AAV1-I2-N/C,[2] cognitively impaired rats 30 female AAV1-GFP,[3] control rats (21 days old)	12 mo	15 AAV1-I2-N/C & 15 AAV1-GFP rats fed 0.1% EHT[4] formulated diet As controls, 15 female AAV1-I2-N/C & 15 female AAV1-GFP pups fed similar diets lacking EHT	Hippocampal-dependent cog function assessed at 6 months: spatial reference memory task in water maze Hippocampal-dependent cog function assessed at 12 months: object location memory task	In the absence of EHT dietary suppl, AAV-I2-N/C rats displayed delayed performance compared w/other groups at 6 mo AAV-I2-N/C rats treated with EHT presented a discrimination ratio ~ 70% vs. non-EHT and control groups at 12 mo	$p = 0.038$ $p < 0.02$
Cao et al. (2011)	Experiment	N = 6-7 per treatment group Aβ PPsw+PS1 Tg mice No treatment mice (6–8 mo old)	3 hrs	Mice injected intraperitoneally with saline, caffeine, un-concentrated coffee (0.3 mg), concentrated coffee (1.5 mg), or concentrated decaffeinated coffee (0.06 mg)	12 cytokines & chemokines measured with Lumenix assay	Only coffee solutions induced increases in GCSF,[5] IL-10,[6] & IL-6,[7] Caffeinated, but not decaf coffee found to ↑ 3-Trial Recall in cog interference task of working memory	Un-concentrated coffee: $p < 0.00001$ Concentrated coffee: $p < 0.05$
Shukitt-Hale et al. (2013)	Experiment	N = 150 male aged rats (19 mo old)	8 wks	**Study I**: rats assigned groups containing 0 (control), 0.165, 0.275, 0.55, or 0.825 % coffee extract **Study II**: rats assigned to (control), 0.387% coffee, 0.0181% caffeine, 0.55% coffee, or 0.0258% caffeine	Motor, spatial learning & memory, & working memory	Coffee at 0.165 % of the diet (3-cup equivalent) improved measures of long-term memory, whereas 0.387 % coffee (7 cups) and 0.55 % coffee (10 cups) improved short-term memory	$p < 0.05$

[1] Aβ PPsw+PS1 = amyloid-β protein precursor with a "Swedish" mutation and presenilin 1, resulting in cognitive impairment and familial form of AD.
[2] AAV1-I2-N/C = adeno-associated virus 1 vector expressing IPP2A 2 N- and C-terminal fragments. PP2A activity results in increased levels of hyperphosphorylated tau and amyloid beta peptide, leading to neurodegeneration and dementia.
[3] AAV1-GFP = adeno-associated virus 1 vector encoding green fluorescent protein
[4] EHT = eicosanoyl-5-hydroxytryptamide
[5] GCSF = granulocyte-colony stimulating factor
[6] IL-10 = interleukin 10, an anti-inflammatory cytokine
[7] IL-6 = interleukin 6, which acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine

performance with higher levels of coffee consumption was observed for all four tests ($p < 0.001$ in each case). However, no distinction was made between caffeinated and decaffeinated coffee.

In a retrospective cohort study, a more specific positive association was found between coffee and cognitive function [25]. Nine hundred and twenty three healthy adults, on whom intelligence quotient data was collected at age 11, were assessed at age 70 using tests measuring general cognitive ability, speed of information processing, and memory. Caffeine consumption was obtained by self-report questionnaire, and it was shown that drinking ground coffee (e.g., filter and espresso) was highly correlated with performance on the National Adult Reading Test ($p=.007$), and the Wechsler Test of Adult Reading ($p = .02$).

Johnson-Kozlow and colleagues [26] assessed coffee consumption and cognitive function in 1,528 older adults (890 women,

mean age 72.6 years). Study subjects reported coffee intake via the Willet Semiquantitative Food Frequency Questionnaire, which assessed lifetime coffee intake in terms of years of use and usual number of cups per day of caffeinated and decaffeinated coffee intake. Cognitive performance was evaluated using 12 standardized tests, among which the MMSE was included. Higher lifetime coffee consumption in women was associated with better ($p \leq 0.05$) performance on six of the 12 tests, of which the majority involved a verbal component. Current caffeinated coffee intake was associated with better performance on only two of the 12 tests ($p < 0.05$). Thus, this study found stronger effects for lifetime as compared with current coffee intake, highlighting the chronic effects of caffeine as distinct from its acute effects.

In a prospective study, Laitala and colleagues [27] failed to find a relation between coffee consumption during middle age and cognitive functioning in old age in a cohort of 2606 middle-aged Finnish twins followed for a median of 28 years. Coffee drinking was assessed by self report in number of cups per day. Cognitive status was defined by using a combination of a screening to identify potential dementia cases (TELE) and the Telephone Interview for Cognitive Status. In this sample, coffee consumption was not an independent predictor of cognitive performance in old age. Also, coffee drinking did not affect the risk of mild cognitive impairment or dementia [27].

Animal experiments

Arendash and colleagues [28] have shown that in AD mice, caffeinated, but not decaffeinated coffee, led to decreased plasma amyloid beta levels, a toxic peptide that accumulates in the brain of patients with AD. These results suggest that moderate caffeine intake (~ 5 cups of coffee per day) might be critical to decreasing blood amyloid beta levels and protect against or treat AD [29]. Additionally, a recent study wherein aged rats were fed various percent coffee diets 8 weeks prior to motor and cognitive behavior assessment found that coffee supplementation at 0.165 % of the diet (3-cup equivalent) improved measures of long-term memory, whereas 0.387 % coffee (7 cups) and 0.55 % coffee (10 cups) improved working and short-term memory, compared to those fed a control diet [30]. However, in a subsequent study, the authors noticed that the effects of caffeine alone did not account for the performance improvements.

Animal experiments by Cao and colleagues, [31] also suggest that coffee contains constituents (aside from caffeine) that may provide cognitive benefits against AD. The effects of caffeinated and decaffeinated coffee on plasma cytokines (related to AD) were compared to those of caffeine alone. Mice treated with caffeinated coffee revealed increased plasma levels of granulocyte-colony stimulating factor (GCSF), IL-10, and IL-6 [31]. These cytokines are thought to trigger long-term beneficial mechanisms against AD (e.g., recruitment of bone marrow cells to increased neurogenesis), and neither caffeine solution alone or decaffeinated coffee provided this cytokine effect.

More recently, a minor component of coffee unrelated to caffeine, eicosanoyl-5-hydroxytryptamide (EHT), was administered to rats for 6-12 months. The results showed substantial amelioration of tau hyperphosphorylation and decreased levels of cytoplasmic amyloid beta protein [32]. Tau hyperphosphorylation refers to the process by which tau proteins become defective and can no longer be involved in stabilizing neuronal microtubules, which generates cell death [33]. Similarly, amyloid beta protein accumulation is another marker of neuronal damage in AD. These findings raise the possibility that EHT may contribute to the neuroprotective benefits associated with coffee consumption.

Discussion

Although the data is mixed, the majority of prospective, cross-sectional, and animal studies suggest some benefit of coffee for protection against memory loss, cognitive decline and/or AD. Caffeine, coffee's most studied ingredient, is known to enhance information processing speed, attention, and reaction time in humans [34]. It can block adenosine receptors and decrease the production of enzymes involved in amyloid formation, thereby preventing the accumulation of amyloid-beta-peptide in and around cerebral blood vessels that result in cognitive deficits [35]. However, it is currently unclear whether caffeine itself is sufficient for reducing AD risk or delaying onset.

The animal studies further suggest that caffeine combines with some as yet unidentified component of coffee to selectively elevate these three plasma cytokines. Given that long-term treatment with coffee (but not decaffeinated coffee) enhanced working memory in a fashion that was associated only with increased plasma GCSF levels, the increase in GCSF is particularly relevant to novel coffee-related therapeutic actions against AD [31]. Additionally, the evidence supporting EHT as means to decrease tau hyperphosphorylation, as well as the buildup of amyloid beta protein, highlights another potentially neuroprotective component of coffee, not present in other caffeinated products [32]. Given the large amount of coffee consumption globally, these results might have important implications for the prevention or delaying the onset of dementia and AD. Despite the inconsistencies addressed across epidemiological studies studying the relationship between coffee consumption and improvements in cognitive function [23,27], animals studies continue to encourage further human experiments and generate testable mechanistic hypotheses.

Limitations

Relatively few human studies were available to address coffee specifically vs. caffeine from various sources. In addition, relatively few studies differentiate between the effects of caffeinated from decaffeinated coffee on AD, which were variables of interest. The studies mentioned generally evaluate an outcome related to, but not specific to incident AD. For prospective studies, follow up periods ranged anywhere between 2 and 28 years. The majority utilized food frequency questionnaires to assess coffee intake, which rely on self-reported data and can both under and overestimate consumption. Similarly, the batteries of standardized tests utilized to assess cognitive performance and onset of AD differed in quality and specificity (MMSE vs. verbal retrieval).

Clinical Recommendations

Further prospective human studies are required before definitive clinical recommendations can be made. That said, coffee is ubiquitous and associated with few adverse events among healthy individuals [15]. While there is yet insufficient evidence to suggest the recommendation of coffee for the prevention or treatment of AD, coffee consumption has been shown to have other health benefits independent of cognitive functioning [36]. From a practical clinical perspective, in those for whom caffeine or coffee is not specifically contraindicated, it would not be unreasonable for clinicians to suggest low to moderate caffeinated coffee consumption (2-4 cups per day) as part of a daily routine. Coffee consumption earlier in the day is advised, as to not negatively affect sleep and possibly assist in management of or reduction of risk for AD. Further research is warranted and future studies should also address potential differences in the effects of caffeinated vs. decaffeinated coffee on cognitive function and AD. Randomized control trials wherein subjects are assigned to caffeine vs. caffeinated coffee vs. decaffeinated coffee vs. placebo may be necessary to establish a causal relation.

Conclusions

While no randomized, prospective trials on coffee and AD have been performed to date, the majority of prospective, cross-sectional, and animal studies suggest a protective association between coffee intake and cognitive function. Based on our review of the literature, we emphasize the need for additional prospective, randomized trials to more adequately assess the effects of caffeinated vs. decaffeinated coffee, and perhaps more specifically other components of caffeinated coffee, on outcomes related to cognitive decline, dementia, and AD. Although there is currently insufficient evidence to warrant clinical recommendations, coffee consumption is generally associated with a low risk profile and may have beneficial effects on cognitive function.

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