

COFFEE, TEA, AND CAFFEINE CONSUMPTION AND PREVENTION OF LATE-LIFE COGNITIVE DECLINE AND DEMENTIA: A SYSTEMATIC REVIEW

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Abstract: A prolonged preclinical phase of more than two decades before the onset of dementia suggested that initial brain changes of Alzheimer's disease (AD) and the symptoms of advanced AD may represent a unique continuum. Given the very limited therapeutic value of drugs currently used in the treatment of AD and dementia, preventing or postponing the onset of AD and delaying or slowing its progression are becoming mandatory. Among possible reversible risk factors of dementia and AD, vascular, metabolic, and lifestyle-related factors were associated with the development of dementia and late-life cognitive disorders, opening new avenues for the prevention of these diseases. Among diet-associated factors, coffee is regularly consumed by millions of people around the world and owing to its caffeine content, it is the best known psychoactive stimulant resulting in heightened alertness and arousal and improvement of cognitive performance. Besides its short-term effect, some case-control and cross-sectional and longitudinal population-based studies evaluated the long-term effects on brain function and provided some evidence that coffee, tea, and caffeine consumption or higher plasma caffeine levels may be protective against cognitive impairment/decline and dementia. In particular, several cross-sectional and longitudinal population-based studies suggested a protective effect of coffee, tea, and caffeine use against late-life cognitive impairment/decline, although the association was not found in all cognitive domains investigated and there was a lack of a distinct dose-response association, with a stronger effect among women than men. The findings on the association of coffee, tea, and caffeine consumption or plasma caffeine levels with incident mild cognitive impairment and its progression to dementia were too limited to draw any conclusion. Furthermore, for dementia and AD prevention, some studies with baseline examination in midlife pointed to a lack of association, although other case-control and longitudinal population-based studies with briefer follow-up periods supported favourable effects of coffee, tea, and caffeine consumption against AD. Larger studies with longer follow-up periods should be encouraged, addressing other potential bias and confounding sources, so hopefully opening new ways for diet-related prevention of dementia and AD.

Key words: Coffee consumption, tea consumption, caffeine use, mild cognitive impairment, dementia, Alzheimer's disease, cognitive disorders, nutrition.

Introduction

The aging of populations globally is the most powerful driver of the increase in age-related disorders, including dementia, Alzheimer's disease (AD), and late-life cognitive disorders, with a profound impact on societies worldwide (1). The 2013 figures suggested that an estimated 5.2 million Americans have AD, with 5 million comprise the older onset AD population (2). In Western countries, the most common forms of dementia are AD and vascular dementia (VaD), with respective frequencies of 70% and 15% of all dementias (3). AD is both multifactorial and heterogeneous, involving aberrant protein processing and is characterized by the presence of both intraneuronal protein clusters composed of paired helical filaments of hyperphosphorylated tau protein [neurofibrillary tangles (NFTs)], and extracellular protein aggregates [senile plaques (SPs)]. The SPs are the result of misprocessing of the amyloid precursor protein (APP), a type-

1 transmembrane protein, by β - and γ -secretases to form a toxic β -amyloid ($A\beta$) peptide of 40–42 amino acids (4) that aggregates and initiates a pathogenic self-perpetuating cascade ultimately leading to neuronal loss and dementia.

In the last decade, lowering the burden of $A\beta$ with a strategy against the production and the accumulation of this peptide have represented a large portion of the many therapeutic approaches currently under development for the treatment of AD (5, 6). However, drugs currently used for the treatment of AD produce limited clinical benefits and do not treat the underlying causes of the disease (7). The causes of dementia and predementia syndromes are, at present, unknown, but some studies have suggested that they may be prevented (8–14). Currently, control of potential risk factors is believed to be the most effective means of preventing dementia, late-life cognitive decline, and mild cognitive impairment (MCI). In fact, epidemiological evidence supported the hypothesis that modifiable vascular, metabolic, and lifestyle-related

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factors were associated to the development of dementia and predementia syndromes in late life (8, 11-13).

At present, one of the most intriguing and appealing links hypothesized in recent years is the association between lifestyle factors such as diet and dietary habits and the occurrence of AD (15-17). Dietary factors may affect the risk of cardiovascular disease, also influencing the risk of AD and dementia (18-20). A growing body of evidence suggested that certain diets have been associated with a lower incidence of AD, so maintaining a healthy diet may have an impact on many of these possible risk factors for cognitive decline, and the model to follow seems to be the Mediterranean diet (MeDi) (14, 19). Therefore, elevated dietary monounsaturated and n-3 polyunsaturated fatty acids and high fish consumption (20, 21), alongside high levels of antioxidants from fruit and vegetables (22, 23), and moderate alcohol consumption (24, 25) may have a beneficial effect on the risk of dementia. Some recent systematic reviews and meta-analyses of pooled studies on this issue found that a higher adherence to the MeDi was associated with a reduced risk of cognitive impairment, MCI and AD, as well as the transition from MCI to AD (14, 26-28).

Among diet-related factors, coffee is one of the most popular drinks in the world, regularly consumed by millions of people and, owing to its caffeine content, it is the best known psychoactive stimulant resulting in heightened alertness and arousal and improvement of cognitive performance (29). Besides its short-term effect, recent epidemiological and experimental studies indicate that caffeine, the main psychoactive component of coffee and tea, when administered chronically, has beneficial effects against a number of acute and chronic neurological disorders including stroke, Parkinson's disease, amyotrophic lateral sclerosis, dementia, and AD (30-34). In particular, animal studies suggested that chronic caffeine consumption may inhibit A β production in brain of rodents (35), improve cognitive performance in animal models of AD (36) or prevent cognitive decline in male rats (37). Caffeine, as an antioxidant substance, was revealed to reduce oxidative stress (38) and also to protect against the disruptions of the blood-brain barrier (BBB) (39). In tea and coffee, other substances different from caffeine might also affect cognition in man, such as theanine that crosses the BBB and is present only in tea and mushroom (40). In this systematic review article, we examined the possible role of coffee and tea consumption and caffeine use in modulating the risk of late-life cognitive impairment/decline, MCI, dementia, and AD, as well as the possible mechanisms behind the observed associations.

Methods

In the present systematic review article, we reviewed clinical and epidemiological reports from the international literature published before January 2014, including both cross-sectional and longitudinal population-based and case-control studies that provided a description of the assessment of coffee, tea,

or caffeine intake/plasma caffeine levels. Furthermore, these studies provided also the diagnostic criteria for the diagnoses of MCI, AD, unspecified dementia or the neuropsychological tools used for defining late-life cognitive impairment/decline. The studies included had to present original data. This systematic review was based upon searches of US National Library of Medicine (PubMed), Ovid MEDLINE, EMBASE, Google Scholar, Web of Science, and Scopus databases by the following terms to identify the risk exposure (coffee OR tea OR caffeine) combined with terms to determine the outcomes of interest [cognitive AND (impairment OR decline OR deterioration) OR Alzheimer's disease OR dementia OR mild cognitive impairment OR MCI]. A search filter was developed to include only human studies. There were no language restrictions on the search. Figure 1 shows the stages in obtaining studies for inclusion in the present report. From 631 articles identified with multiple electronic searches, we screened titles and abstracts of the citations downloaded from the searches identifying 175 potential relevant articles chosen for a closer review. Excluding other 126 articles not meeting inclusion criteria, we obtained full copies of the 49 potentially suitable reports for further assessment. After inclusion of 8 articles of interest from the reference lists of the selected articles and exclusion of other 29 articles, 28 studies met study eligibility criteria, and were finally included in the overall systematic review (41-68) (Tables 1 and 2).

Coffee, tea, and caffeine consumption and late-life cognitive impairment/decline

Cross-sectional studies

Among self-selected coffee or tea drinkers for many years, several cross-sectional (41-50) and longitudinal (44, 51-61) population-based studies suggested a protective effect of coffee, tea, and caffeine use against cognitive impairment/decline (Table 1). However, apart one study with participants of a younger age than other reports (41), in studies with an extensive neuropsychological assessment, the association was not found in all cognitive domains investigated. In fact, among cross-sectional studies, the Health and Lifestyle Survey on 9,003 British adults with a mean age <50 years reported a dose-response trend for increasing levels of coffee consumption in all administered neuropsychological tests assessing simple reaction time, choice reaction time, incidental verbal memory, and visuo-spatial skills (41). On the contrary, in the Rancho Bernardo Study (42), including 1,538 participants aged 52-98 years from Southern California, higher lifetime caffeine intake was associated with better performance on 6 of 12 neuropsychological tests assessing short- and long-term memory of spoken words, long-term memory for geometric forms, fluency, and orientation, registration attention, language, calculation, and recall, and borderline associated with two other cognitive tests assessing concentration and short-term memory for geometric forms only in women. Among women aged >

Table 1
Cross-sectional and longitudinal population-based and case-control studies of coffee, tea, and caffeine consumption and plasma levels of caffeine in relation to cognitive impairment, cognitive decline, and mild cognitive impairment (MCI) in older subjects included in the systematic review

Reference	Study design, setting, and subjects	Coffee, tea, or caffeine consumption/plasma caffeine levels	Assessment of cognition or diagnosis of dementia	Covariates	Principal findings
<i>Cross-sectional studies</i>					
Jarvis 1993 (41) The Health and Lifestyle survey UK	Cross-sectional, population-based on 9,003 British adults with a mean age <50 years	Mean caffeine consumption ranged from approximately 400–575 mg/day ^a	Cognitive function was assessed with 4 simple tasks of simple reaction time, choice reaction time, incidental verbal memory, and visuo-spatial reasoning	Coffee/tea consumption, age, sex, class, educational level, housing tenure, retired, not working through disability, self-rated overall health and current psychological malaise score, and use of alcohol, tobacco and tranquillisers	Increased levels of coffee and tea consumption were associated with improved performance on all cognitive tests. The effects were strongest in relation to coffee, but were also found with tea, and when coffee and tea consumption were combined into an overall caffeine intake scale, with a dose response relationship to increasing levels of consumption.
Johnson-Kozlow et al., 2002 (42) The Rancho Bernardo Study USA	Cross-sectional, population-based on 1,538 participants aged 52–98 years from Southern California	Mean caffeinated coffee consumption calculated to be 2.3 cups/day for men and 2.0 cups/day for women ^b	Cognitive skills assessed with 12 measures: total recall, short- and long-term recall of the BSKT; copying, immediate and delayed recall of the HVRT; MMSE total score and Serial 7's and "World" Backwards; Blessed Items; TMT-B; and CF Test	For women, age, education, and ever use of estrogens. For men, age, education, and the use of antihypertensive drugs	Higher lifetime caffeine intake was associated with better performance on 6 of 12 neuropsychological tests assessing short- and long-term memory of spoken words, long-term memory for geometric forms, fluency, and orientation, registration attention, language, calculation, and recall, and borderline associated with two other cognitive tests assessing concentration and short-term memory for geometric forms only in women
Kuriyama et al., 2006 (43) The Tsurugaya Project Japan	Cross-sectional, population-based on 2,730 people aged >70 years	16.9% consumed < 3 cups green tea /week; 10.8% consumed 4–6 cups/week or 1 cup/day, and 72.3% consumed > 2 cups/day ^c	Cognitive abilities assessed with MMSE	Age, sex, consumption of green tea/black or oolong tea/coffee, presence or absence of diabetes mellitus, presence or absence of hypertension, history of stroke, depressive symptoms, duration of education, visiting friends, energy intake, intake of non-dietary vitamin C or E, and consumption of fish	An inverse dose-response relations between consumption of green tea and the prevalence of cognitive impairment was found. In contrast, a weak or null relation between consumption of black or oolong tea or coffee and cognitive impairment was observed
Ng et al., 2008 (44) The Singapore Longitudinal Ageing Studies (SLAS) Chinese living in Singapore	Cross-sectional and longitudinal (1–2 years), population-based on 2,501 people aged >55 years	67%–70% drank less than 1 cup /week; 12%–15% drank more than 1 cup/week but less than 1 cup/day; 18%–19% drank ≥1 cup/day ^d	Cognitive abilities assessed with MMSE	Age, gender, education, smoking, alcohol consumption, BMI, hypertension, diabetes, heart diseases, stroke, depression, APOE ε4, physical activities, social and productive activities, vegetable and fruit consumption, fish consumption, daily coffee consumption, baseline MMSE score, interval between baseline and follow-up	More frequent tea consumption of all kinds was associated with a lower risk of cognitive impairment

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Table 1 (continued)

Chin et al., 2008 (45) The Dublin Healthy Ageing Study Ireland	Cross-sectional, population- based on 466 people aged >65 years	Mean tea consumption calculated to be 4.5 cups/day ^a	Cognitive function assessed with MMSE and a global composite score obtained from the average of the sum of the standardised scores of NART, WAIS-III digit symbol coding, CF, VF, WMS—III serial word lists, letter number sequencing, and revised visual reproduction	Age, gender, education, social class, alcohol, tea intake, depression, life satisfaction, hypertension, use of psychotropic medications, smoking, stroke, fruit intake	Global composite cognition scores in this community- dwelling, non-demented elderly population were positively correlated with tea intake
Nurk et al., 2009 (46) The Hordaland Health Study (HUSK) Norway	Cross-sectional, population -based on 2,031 participants aged 70–74 years	Mean intake was 222 mL/day for tea. When nonconsumers were excluded, the mean intake doubled: 417 mL/day for tea	Cognitive abilities assessed with KOLT, TMT-A, WAIS-III mDST, WAIS-III BD, MMSE, and COWAT	Sex, education, history of cardiovascular disease, smoking status, vitamin supplement use, diabetes, and total energy intake	An habitual intake of tea was associated with better performance in semantic memory, visual attention, and perceptual speed, but not in episodic memory, visuo-spatial skills, and global cognition
Huang et al., 2009 (47) Project of Longevity and Aging in Duijiangyan (PLAD) China	Cross-sectional, population- based on 681 nonagenarians- centenarians aged 90 to 108 years	Subjects were asked whether they had ever had habits of tea consumption, and 1 of 3 answers was recorded: never, did in the past, or currently. Information was obtained on the average frequency of drinking tea, and on the number of years they had did for. Tea consumption included all types of tea.	Cognitive abilities assessed with MMSE	Age, sex, sleep habits, educational levels, religion habits and temperament	Cognitive impairment was associated with lower prevalence of tea consumption in men but not in women
Corley et al., 2010 (48) The Lothian Birth Cohort 1936 Study Scotland	Cross-sectional, population -based on 923 participants, aged 70 years	Mean caffeine consumption ranged from approximately 182.5 mg/day ^a	Cognitive abilities assessed with MMSE, WAIS-III, WMS—III, NART, and WTAR	Age, sex, occupational social class, and age 11 intelligence quotient	In age- and sex- adjusted models, significant positive associations was found between caffeine intake and global cognitive functions and memory. After adjustment for age 11 intelligence quotient and social class, most of the positive associations in non-completely adjusted models became non significant
Wu et al., 2011 (49) 2005 National Health Interview Survey Taiwan	Cross-sectional, population -based on 2,119 participants aged > 65 years	20.7% less than 1 cup of coffee/ week, 12.5% more than 1 cup of coffee/week, 68.8% were non-coffee drinkers; 17.6% less than 1 cup of tea/week; 46.1% more than 1 cup of tea/week; 36.3% were non-tea drinkers ^a	Cognitive abilities assessed with MMSE	Age, gender, education, marital status, social support, stroke, leisure -time physical activity, hyperlipidemia, tea intake, depressive symptoms, smoking, stroke, fruit and vegetables intake, multivitamin intake, self-rated health, physical function and BMI	Older persons who drank coffee one or more times per week had a lower risk of global cognitive impairment than non-coffee drinkers
Valls-Pedret et al., 2012 (50) PREvencion con Dieta MEDiterranea (PREDIMED) study Spain	Cross-sectional on community -dwelling on 447 participants with a mean age of 69.9 years	Median coffee intake of 21 mL/day	Cognitive abilities assessed with MMSE, immediate and delayed recall of RAVLT, the verbal paired associates test of the WMS, the SVF test; the digit span test of WAIS, and the CTT (part I and II)	Age, gender, education years, BMI, current smoking, physical activity, APOE genotype, diabetes, hypertension, and hyperlipidemia	Intake of coffee was associated with better performance in the delayed recall of episodic verbal memory

Table 1 (continued)

Longitudinal studies					
Lammi et al., 1989 (51) Finnish cohort of the Seven Countries Study and other Finnish cohorts Finland	Longitudinal (25 years), population-based on 716 men aged 65-84 years	Coffee consumption measured with 0, 1, 2, 3, 4, >4 cups of coffee /day with 85 mg of caffeine/cup. No data available of mean coffee or caffeine consumption	Cognitive function assessed with the MSQ	Not specified	Low coffee consumption at baseline was associated with reduced cognitive decline
van Bortel et al., 2003 (52) The Maastricht Aging Study (MAAS) The Netherlands	Longitudinal (6 years), population-based on 1,376 participants aged 24-81 years	Mean caffeine consumption ranged from approximately 340–550 mg/day ^a	Cognitive function assessed with VVLT, MCRT, LDST, CF, CST, and SCWT	Age, gender, education, housing, occupation, smoking, alcohol consumption, perceived health	There were small albeit significant associations between the overall estimated caffeine intake at baseline and the 6-year change in complex motor speed (MCRT)
van Gelder et al., 2007 (53) The Finland, Italy, and The Netherlands Elderly (FINE) Study Finland, Italy, and The Netherlands	Longitudinal (10 years), population-based on 676 “elderly” participants	Mean coffee consumption calculated to be 2.2 cups/day ⁱ	Cognitive function assessed with MMSE	Age, education, country, alcohol consumption, smoking status, physical activity, baseline cognitive functioning	A J-shaped association between coffee consumption (3 cups of coffee/day) and cognitive decline was found in this population of healthy elderly men
Ritchie et al., 2007 (54) The Three City Study France	Longitudinal (4 years), population-based on 7,017 participants aged > 65 years	Mean caffeine consumption calculated to be 176 mg/day for men and 186 mg/day for women ⁱ	Cognitive function assessed with MMSE, BVRT, and the Isaacs Set Test	Age, gender, study center	Less cognitive decline found in aged French women whose daily caffeine intake was equivalent to 3+ cups of coffee
Ng et al., 2008 (44) The Singapore Longitudinal Ageing Studies (SLAS) Chinese living in Singapore	Cross-sectional and longitudinal (1-2 years), population-based on 2,501 people aged >55 years	67%–70% drank less than 1 cup/ week; 12%–15% drank more than 1 cup/week but less than 1 cup/day; 18%–19% drank≥1 cup/day ⁱⁱ	Cognitive abilities assessed with MMSE	Age, gender, education, smoking, alcohol consumption, BMI, hypertension, diabetes, heart diseases, stroke, depression, APOE ε4, physical activities, social and productive activities, vegetable and fruit consumption, fish consumption, daily coffee consumption, baseline MMSE score, interval between baseline and follow-up	More frequent tea consumption of all kinds was associated with less cognitive decline
Laitala et al., 2009 (55) The Finnish Twin Cohort Study Finland	Longitudinal (28 years), population-based on 2,606 participants aged 46-52 years	Mean coffee consumption for both men and women calculated to be 5.4 cups/day ⁱⁱⁱ	Cognitive function assessed with TELE and TICS	Education, age, gender	The main finding was the lack of any association between coffee drinking in middle age and cognitive performance in old age beyond a median follow-up of 28 years
Santos et al., 2010 (56) Portugal	Longitudinal (5 years), population-based on 648 participants aged > 65years	Caffeine intake medians were 32 mg/day for women and 33 to 52 mg/day for men ^{iv}	Cognitive function assessed with MMSE	Age, education, smoking, alcohol intake, hypertension, diabetes, obesity, and likely to be related to caffeine consumption (especially through coffee intake)	Caffeine intake (>62 mg/day vs. <22 mg/day) was associated with a lower risk of cognitive decline in women only
Arab et al., 2011 (57) The Cardiovascular Health Study (CHS) USA	Longitudinal (7.9 years), population-based on 4,809 participants aged 65 and older	Mean coffee consumption 0.95 cups/day; mean tea consumption 0.57 cups/day	Cognitive function assessed with MMSE, BVRT, and the Isaacs Set Test	Age at baseline, gender, race, Educational attainment, field center, diabetes, hypertension, current smoking, history of stroke, history of coronary heart disease, depressive symptoms, and APOE ε4 allele	A modestly reduced rates of cognitive decline for some, but not all levels of coffee and tea consumption for women was found

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Table 1 (continued)

<p>Gelber et al., 2011 (58) The Honolulu-Asia Aging Study (HAAS) USA</p>	<p>Longitudinal (25 years), nested case-control study on 3,734 Japanese American men, mean age 52 years at cohort entry, 1965–1968, including 418 decedents who underwent brain autopsies</p>	<p>Mean caffeine intake in midlife was 276 mg among the 154 decedents with microvascular ischemic lesions, as compared to 333 mg among the 121 decedents without any lesions</p>	<p>Cognitive impairment diagnosed with CASI and incident diagnoses of overall dementia with DSM- III-R criteria, probable or possible AD with NINCDS/ADRDA criteria, and VaD with CADDTC criteria</p>	<p>Age, physical activity index, smoking, years of education, hypertension, elevated cholesterol, plus APOE ε4 status, BMI, alcohol consumption, number of childhood years spent in Japan, history of diabetes mellitus, cardiovascular disease, occupational complexity, and marital status</p>	<p>There were no significant associations between coffee or caffeine intake and risk of cognitive impairment, overall dementia, AD, VaD, or moderate/high levels of the individual neuropathological lesion types. However, men in the highest quartile of caffeine intake (>277.5 mg/d) were less likely than men in the lowest quartile (≤ 115.5 mg) to have any of the lesion types</p>
<p>Feng et al., 2012 (59) The Chinese Longitudinal Healthy Longevity Survey (CLHLS). China</p>	<p>Longitudinal population-based (7 years) on 7,139 participants aged 80 to 115 years</p>	<p>Report of past frequency of tea drinking at around age 60 as well as current frequency of tea drinking. The frequency was recorded as “almost every day” or “occasionally” or “rarely or never”.</p>	<p>Cognitive abilities assessed with verbal fluency test</p>	<p>Age, sex, years of schooling, physical exercise (regular exercise vs. others) and activities score</p>	<p>Daily tea drinking was associated with better cognitive function measured by verbal fluency test during a 7-year follow-up period</p>
<p>Cao et al., 2012 (61) Multisite study from the Miami and Tampa areas USA</p>	<p>Longitudinal (2.4 years), case-control on 124 randomly- selected subjects aged 65 and 88 years at study onset, with the Miami cohort (81 subjects) and the Tampa cohort (43 subjects)</p>	<p>Mean plasma caffeine levels at baseline were approximately: 1750 ng/ml for cognitively normal 1750 ng/ml for cognitively normal subjects; 900 ng/ml for MCI subjects; and 1000 ng/ml for patients with dementia</p>	<p>Diagnoses of MCI and overall dementia</p>	<p>Not specified</p>	<p>Plasma caffeine levels greater than 1200 ng/ml in MCI subjects were associated with no conversion to dementia during the ensuing 2–4 year follow-up period</p>
<p>Vercambre et al., 2013 (60) The Women's Antioxidant Cardiovascular Study USA</p>	<p>Longitudinal (5 years), population-based on 2,475 women aged 65 years and over</p>	<p>The highest quintile was equivalent to the amount of caffeine in approximately 4 cups of coffee (>371 mg/day), while lowest quintile of usual caffeine intake was < 30 mg/day</p>	<p>Primary outcome was change in global cognitive score, which was the average of the z- scores of TICS, MMSE, TICS 10-word list (immediate and delayed recall), EBMT (immediate and delayed recall), and CF</p>	<p>Age at initial cognitive assessment, education and energy from diet, marital status, alcohol intake, physical activity, use of multivitamin supplements, smoking, BMI, postmenopausal hormone therapy, aspirin use, non-steroidal anti-inflammatory drug use, history of depression, cardiovascular profile at baseline, diabetes, hypertension, hyperlipidemia, dietary intakes of vitamin C, vitamin E, carotene, vitamin B6, vitamin B12, and folates</p>	<p>Higher caffeine intake (>371 mg/ day, approximately 4 cups of coffee/day) was related to moderately better cognitive maintenance over 5 years in older women with vascular disorders</p>

a. Calculated from Figure 1 of article; b. Calculated from “Current caffeinated coffee consumption/Cups per week” in Table 1 of article; c. Green tea consumption read from Table 1 of article; d. Black or oolong tea consumption read from Table 1 of article; e. Tea consumption read from Table 1 of article; f. Caffeine consumption read from Table 1 of article; g. Coffee and tea consumption read from Table 1 of article; h. Read from Figure 1 of article; i. Calculated from “Categories of daily coffee consumption” in Table 2 of article. Five cups assumed for category “ >4 cups”; j. Calculated from Table 1 of article. Categories calculated as: 0, 1 units = 50 mg; 1, 2 units = 150 mg; 2, 3 units = 250 mg; and >3 units = 350 mg; m. Calculated from Table 1 of article. Categories calculated as: 0–3 cups/day = 1.5 cups/day; 3.5–8 cups/day = 5.75 cups/day; and ≥ 8 cups/day = 10 cups/day; n. Calculated from Figure 1a of article; BSRT: Buschke Selective Reminding Test; HVRT: Heaton Visual Reproduction Test; MMSE: Mini-Mental State Examination; TMT-B: Trail-Making Test-B; BMI: body mass index; APOE: apolipoprotein E; CF: category fluency; WAIS: Wechsler Adult Intelligence Scale; VF: verbal fluency; WMS: Wechsler Memory Scale; NART-R: National Adult Reading Test; KOLT: Kendrick Object Learning Test; TMT-A: Trail Making Test-A; mDST: modified versions of the Digit Symbol Test; BD: Block Design; COWAT: Controlled Oral Word Association Test; WTAR: Wechsler Test of Adult Reading; RAVLT: Rey auditory verbal learning test; SVF: semantic verbal fluency; CTT: Color Trail Test; MSQ: Mental Status Questionnaire; VVLT: Visual Verbal Learning Test; MCRT: Motor Choice Reaction Test; LDST: Letter-Digit Substitution Test; CST: Concept Shifting Test; SCWT: Stroop Color-Word Test; BVRT: Benton Visual Retention Test; TELE: screen to identify potential dementia cases; TICS: Telephone Interview for Cognitive Status; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; AD: Alzheimer's disease; VaD: vascular dementia; CASI: Cognitive Abilities Screening Instrument; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, third edition, revised; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; CADDTC: California Alzheimer's Disease Diagnostic and Treatment Centers; EBMT: East Boston Memory Test

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80 years, the Rancho Bernardo Study failed to find significant association between lifetime coffee consumption and better performance in 11 of the 12 cognitive tests (42). Furthermore, in the Lothian Birth Cohort Study, cognitive function was assessed at age 70 years using tests measuring global cognitive functions, speed of information processing, and memory skills (48). In this study, in age- and sex- adjusted models, significant positive associations were found between caffeine intake and global cognitive functions and memory; however, after adjustment for age 11 intelligence quotient score and social class, most of the positive associations in non-completely adjusted models became non-significant (48). In Norway, in the Hordaland Health Study (HUSK), in the fully adjusted models, an habitual intake of tea was associated with better performance in semantic memory, visual attention, and perceptual speed, but not in episodic memory, visuo-spatial skills, and global cognition (46). Among other cross-sectional population-based studies using composite cognitive scores or global measure of cognitive performance, in Northern Europe, global cognition scores among community-dwelling nondemented older adults in Dublin were positively correlated with tea intake (45). Furthermore, Asian studies of tea and cognition have also reported less global cognitive impairment among former tea drinkers, as evidenced in 2,501 community-living Chinese adults aged >55 years in the cross-sectional component of the Singapore Longitudinal Ageing Studies (SLAS) cohort (44), and in 2,730 people aged >70 years from the Tsurugaya Project in Japan (43). In the Project of Longevity and Aging in Dujiangyan (PLAD), cognitive impairment was associated with lower prevalence of tea consumption in men but not in women among 681 Chinese nonagenarians/centenarians (47). Furthermore, data from 2,119 persons aged 65 years and over who participated in the 2005 National Health Interview Survey in Taiwan suggested that older persons who drank coffee one or more times per week had a lower risk of global cognitive impairment than non-coffee drinkers (49). Finally, in the PREvencion con Dieta MEDiterranea (PREDIMED) study, a cross-sectional evaluation of dietary habits and cognitive function in older persons at high cardiovascular risk living in Spain, the intake of coffee was associated with better performance in the delayed recall of episodic verbal memory (50). All these cross-sectional studies, however, are vulnerable to multiple biases, including the possibility that the drinking behavior of coffee or tea may be a result of cognitive status instead of causally related (69).

Longitudinal studies

Early longitudinal studies reported an inverse and J-shaped association between coffee consumption (3 cups of coffee/day) and cognitive decline in a population of healthy elderly men from three European countries (Finland, Italy, and Netherlands) (53), and significantly less cognitive decline in aged French women whose daily caffeine intake was equivalent to 3+ cups of coffee (54). In fact, in the Finland, Italy and The Netherlands

Elderly (FINE) Study, conducted on 666 men from the cohorts of the Seven Countries Study using the Mini-Mental State Examination (MMSE), coffee consumers had a reduced cognitive decline respect to non-consumers in a 10-year follow-up (53). Similarly, in a study conducted on 716 men from eastern and south-western Finland in connection with the east-west study, which was the Finnish cohort of the Seven Countries Study, low coffee consumption was associated with reduced cognitive decline measured with the Mental Status Questionnaire (MSQ) in a 25-year follow-up (51). Furthermore, in the Three City Study, enrolling about 7,000 participants aged 65 and over, the cognitive examination consisted of three tests and a significant association between daily intake of caffeine and cognitive decline was observed in French women only in relation to verbal retrieval (Isaacs Set Test) and to a lesser extent in visuo-spatial memory (Benton Visual Retention Test) over a 4-year follow-up (54). In a cohort of Portuguese subjects, caffeine intake (>62 mg/day vs. <22 mg/day) was associated with a lower risk of cognitive decline evaluated with MMSE in women with a median follow-up of 4 years (56). Findings from the Cardiovascular Health Study (CHS) on 4,809 participants aged 65 and older also suggested a modestly reduced rates of cognitive decline assessed with the modified MMSE (3MS) over a median follow up of 7.9 years for some, but not all, levels of coffee and tea consumption for women (57). Furthermore, for 2,475 women aged 65+ years in the Women's Antioxidant Cardiovascular Study, higher caffeine intake (approximately 4 cups of coffee/day) was related to moderately better cognitive maintenance over 5 years in older women with vascular disorders (60). Finally, also in the longitudinal component of the SLAS, a more frequent tea consumption of all kinds was associated with a lower risk of cognitive decline in a follow-up of 1-2 years (44), while in the Chinese Longitudinal Healthy Longevity Survey (CLHLS), daily tea drinking was associated with better cognitive function measured by verbal fluency test during a 7-year follow-up period on 7,139 participants aged 80 to 115 years (59). Notwithstanding this substantial body of evidence suggesting a neuroprotective effect of coffee, tea, and caffeine use against cognitive impairment/decline (44, 51, 53, 54, 56, 57, 59), three prospective nested case-control and population-based studies did not find any association between coffee consumption and cognitive decline (52, 55, 58). In the Maastricht Aging Study (MAAS), 1,376 participants aged between 24 and 81 years were cognitively reassessed after 6 years, and there were small albeit significant associations between the overall estimated caffeine intake at baseline and the 6-year change in complex motor speed (motor choice reaction time) (52). Furthermore, in a nested case-control study, 3,494 men from the Honolulu-Asia Aging Study (HAAS) (mean age 52 years at cohort entry, 1965–1968) were examined for dementia in a 25-year follow-up, including 418 decedents who underwent brain autopsy. There were no significant associations between coffee or caffeine intake and risk of cognitive impairment,

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overall dementia, AD, VaD, or moderate/high levels of the individual neuropathological lesion types. However, men in the highest quartile of caffeine intake (>277.5 mg/d) were less likely than men in the lowest quartile (≤ 115.5 mg) to have any of the lesion types (AD lesions, microvascular ischemic lesions, cortical Lewy bodies, hippocampal sclerosis, generalized atrophy) (58). The Finnish Twin Cohort Study from a cohort of like-sexed Finnish twin pairs did not find any association between coffee drinking in midlife and cognitive performance, MCI, or dementia in old age (70). On the other hand, in this Finnish study, dementia and MCI cases were diagnosed with these two screens administered by telephone and not with current clinical criteria, and because cognitive performance was estimated at one time point, Laitala and colleagues were unable to test whether coffee consumption affected the degree or rate of cognitive decline (55). Moreover, for the MCI construct, a recent case-control study showed that high plasma caffeine levels in MCI patients at the beginning of a 2–4 year cognitive assessment period were associated with complete avoidance of progression to dementia over that period (61). A systematic review and meta-analysis of Santos and colleagues of caffeine and cognitive decline conducted on nine cohort and two case-control studies published up to September 2009 reported a non-significant relative risk (RR) of 0.98 [95% Confidence Interval (CI): 0.87–1.11] (34). However, a very recent systematic review of six selected longitudinal population-based studies on tea, coffee, or caffeine consumption and cognitive decline (44, 52–54, 56, 57) suggested that for all studies of tea and most studies of coffee and caffeine, the estimates of cognitive decline were lower among consumers (69). This systematic review found modestly reduced rates of cognitive decline over median follow-up times ranging from 1.3 to 10 years, although there was a lack of a distinct dose response, with a stronger effect among women than men (69).

Dementia and Alzheimer's disease prevention and coffee, tea, and caffeine consumption

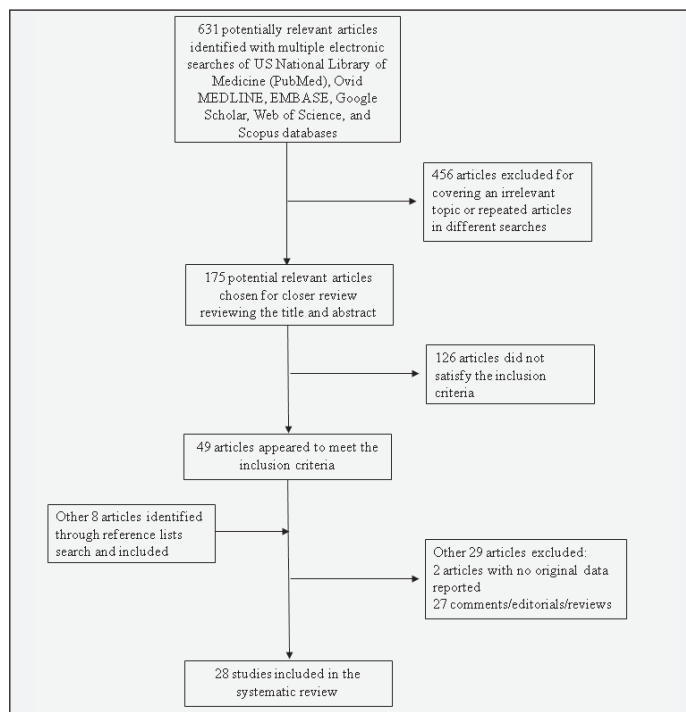
Cross-sectional studies

There was a growing body of epidemiological evidence supporting a neuroprotective role of coffee, tea, and caffeine use against cognitive impairment/decline (41–61), on the contrary, a lower number of case-control (58, 61–63) and population-based studies (55, 64–68) analyzed the long-term effects of coffee, tea, or caffeine consumption and plasma levels of caffeine on dementia and AD (Table 2). The findings of the first study, involving 170 cases and 170 controls from Australia, although well designed and carefully executed, were not in favour of a protective effect of coffee or tea consumption against AD (62). However, the case-control study assessed many possible risk factors and the interview lasted 2 hours, with some concerns regarding information bias. In addition, the risk of coffee or tea consumption was not adjusted for other possible risk factors and finally, among

the 87 variables examined, only ten resulted in statistically significant odds ratios (ORs), and only four were proposed, for biological plausibility and statistical robustness, as possible AD risk factors (history of dementia, probable AD, or Down's syndrome in a 1st-degree relatives, and underactivity as a behavioural trait in both the recent and more distant past) while among environmental exposures the study did not identify any other risk factor for AD (62). The findings of a successive case-control study conducted in Portugal on 54 cases and 54 controls have demonstrated protection of caffeine intake against AD (OR: 0.40, 95% CI: 0.25–0.67), although these results were based on a small hospital-based case-control study (63). The other two recent case-control studies were described in detail above and were the nested case-control of the HAAS with a neuropathological component (58) and the interesting study investigating plasma caffeine levels and risk of dementia or progression of MCI to dementia (61).

Figure 1

Flow-chart of retrieved and selected articles showing associations among coffee, tea, and caffeine consumption and late-life cognitive/impairment decline, dementia, and Alzheimer's disease



Longitudinal studies

For dementia prevention, the population-based studies available were all longitudinal (55, 64–68). The results of a longitudinal population-based study in Canada, the Manitoba Study of Health and Aging (MSHA), did not show that coffee or tea consumption was inversely associated with AD risk in a 5-year follow-up (64). On the contrary, findings from the Canadian Study of Health and Aging (CSHA) on 4,615 subjects

Table 2
Cross-sectional and longitudinal population-based and case-control studies on the relationships among coffee, tea, and caffeine consumption and plasma levels of caffeine and dementia and Alzheimer's disease (AD) included in the systematic review

Reference	Study design, setting, and subjects	Coffee, tea, or caffeine consumption/plasma caffeine levels	Assessment of cognition or diagnosis of dementia	Covariates	Principal findings
<i>Cross-sectional studies</i>					
Broe 1990 (62) Australia	Cross-sectional, 170 case-control on AD patients and 170 controls	Never drank tea or coffee and > 4 cups of tea or coffee daily sometime in life were the categories of consumption proposed in this study	Diagnosis of possible or probable AD with NINCDS-ADRDA criteria for the selected cases.	Age and sex (matching)	The study results were not in favour of a protective effect of coffee or tea consumption against AD.
Maia and de Mendonça, 2002 (63) Portugal 5	Cross-sectional, case-control on 4 AD patients and 54 controls	AD patients had an average daily caffeine intake during the 20 years that preceded diagnosis of AD of 73.9 ± 97.9 mg, whereas the controls had an average daily caffeine intake of 198.7 ± 135.7 mg during the corresponding 20 years of their lifetimes	Diagnosis of probable AD with NINCDS-ADRDA criteria for the selected cases and cognitive assessment for the controls with MMSE	Age and sex (matching), hypertension, diabetes, stroke, head trauma, smoking habits, alcohol consumption, non-steroid anti-inflammatory drugs, vitamin E, gastric disorder, heart disease, education and family history of dementia	Caffeine intake was associated with a significantly lower risk for AD, independently of other possible confounding variables
<i>Longitudinal studies</i>					
Tyas et al., 2001 (64) The Manitoba Study of Health and Aging (MSHA) Canada	Longitudinal (5 years), population-based on 1,039 participants aged >65 years	Regular ("nearly every day") vs. non-regular coffee or tea consumption	Cognitive screening with the 3MS and incident diagnosis of possible or probable AD with NINCDS-ADRDA criteria	Age, gender, education	Coffee or tea consumption was not inversely associated with AD risk in a 5-year follow-up
Lindsay et al., 2002 (65) The Canadian Study of Health and Aging (CSHA) Canada	Longitudinal (5 years), population based on 4,615 participants aged >65 years	Daily vs. not daily coffee or tea consumption	Cognitive screening with the 3MS and incident diagnoses of AD with DSM-IV criteria and VaD with NINDS/AIREN criteria	Age, gender, education	Coffee consumption, but not tea drinking, was associated with a reduced risk of AD in a 5-year follow-up
Laurin et al., 2004 (66) The Honolulu-Asia Aging Study (HAAS) USA	Longitudinal (30.2 years), population-based on 2,459 Japanese American men, mean age 52 years at cohort entry, 1965–1968	Mean intake of tea (black and green); flavonoid intake was estimated from 11 types of tea infusions	Cognitive impairment diagnosed with CASI and incident diagnoses of overall dementia with DSM-III-R criteria, probable or possible AD with NINCDS/ADRDA criteria, and VaD with CADDTC criteria	Socio-demographic and lifestyle factors, cardiovascular risk factors, other dietary constituents, APOE $\epsilon 4$ allele	No effect of tea intake on incident risk of dementia and AD
Dai et al., 2006 (67) The Kame Project USA	Longitudinal (6.3 years), population-based on 1,836 participants aged > 65 years	Usual intake of tea (8 frequency options and 3 usual portion sizes; categorization to < 1/week, 1–2/week, > 3/week)	Cognitive function assessed with CASI and incident diagnosis of probable AD with NINCDS/ADRDA criteria	Age, gender, education, physical activity, BMI, baseline CASI score, olfaction diagnostic group, total energy intake, intake of SFAs, MUFAs and PUFAs, APOE, smoking, alcohol drinking, supplementation of vitamins C, E and multivitamin, dietary intake of vitamins C, E and β -carotene	No effect of tea consumption on incident risk of AD

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Table 2 (continued)

Eskelinen et al., 2009 (68) The Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Study Finland	Longitudinal (21 years), population-based on 1,409 people mean age at baseline 50.4 years	60.5% did not drink tea, and 80% of tea drinkers consumed 1, 2 cups per day. Mean coffee consumption calculated to be 4.3 cups/day ^a	Cognitive screening with the MMSE and incident diagnoses of dementia with DSM-IV criteria and probable or possible AD with NINCDS/ADRDA criteria	Age, gender, education, follow-up, residence, midlife smoking, SBP, serum total cholesterol, BMI, physical activity	Decreased risk of dementia by 65% and AD by 64% with daily coffee drinking of 3–5 cups. No effect for tea consumption on dementia/AD risk was reported
Laitala et al., 2009 (55) The Finnish Twin Cohort Study Finland	Longitudinal (28 years), population-based on 2,606 participants aged 46–52 years	Mean coffee consumption for both men and women calculated to be 5.4 cups/day ^a	Cognitive function assessed with TELE and TICS and dementia and MCI diagnoses obtained with the same screening tools	Education, age, gender	The main finding was the lack of any association between coffee drinking in middle age and cognitive performance (including MCI and dementia) in old age beyond a median follow-up of 28 years
Gelber et al., 2011 (58) The Honolulu-Asia Aging Study (HAAS) USA	Longitudinal (25 years), nested case-control study on 3,734 Japanese American men, mean age 52 years at cohort entry, 1965–1968, including 418 decedents who underwent brain autopsy	Mean caffeine intake in midlife was 276 mg among the 154 decedents with microvascular ischemic lesions, as compared to 33 mg among the 121 decedents without any lesions	Cognitive impairment diagnosed with CASI, diagnoses of overall dementia, AD, and VaD	Age, physical activity index, smoking, years of education, hypertension, elevated cholesterol, plus APOE ε4 status, BMI, alcohol consumption, number of childhood years spent in Japan, history of diabetes mellitus, cardiovascular disease, occupational complexity, and marital status	There were no significant associations between coffee or caffeine intake and risk of cognitive impairment, overall dementia, AD, VaD, or moderate/ high levels of the individual neuropathological lesion types. However, men in the highest quartile of caffeine intake (>277.5 mg/d) were less likely than men in the lowest quartile (≤115.5 mg) to have any of the lesion types
Cao et al., 2012 (61) Multisite study from the Miami and Tampa areas USA	Longitudinal (2–4 years), case -control on 124 randomly- selected subjects aged 65 and 88 years at study onset, with the Miami cohort (81 subjects) and the Tampa cohort (43 subjects)	Mean plasma caffeine levels at baseline were approximately: 1750 ng/ml for cognitively normal subjects; 900 ng/ml for MCI subjects; and 1000 ng/ml for patients with dementia ^a	Diagnoses of MCI and overall dementia	Not specified	Plasma caffeine levels greater than 1200 ng/ml in MCI subjects were associated with no conversion to dementia during the ensuing 2–4 year follow-up period

a. Calculated from Table 1 of article. Categories calculated as: 0–2 cups/day = 1 cup/day; 3–5 cups/day = 4 cups/day; and ≥5 cups/day = 6 cups/day; b. Calculated from Table 1 of article. Categories calculated as: 0–3 cups/day = 1.5 cups/day; 3.5–8 cups/day = 5.75 cups/day; and ≥8 cups/day = 10 cups/day; c. Calculated from Figure 1a of article; NINCDS-AD/RA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; MMSE: Mini-Mental State Examination; 3MS: modified Mini-Mental State Examination; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; VaD: vascular dementia; NINDS/AIREN: National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, third edition, revised; CADDTC: California Alzheimer's Disease Diagnostic and Treatment Centers; APOE: apolipoprotein E; CASI: Cognitive Abilities Screening Instrument; SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; SBP: systolic blood pressure; BMI: body mass index; TELE: screen to identify potential dementia cases; TICS: Telephone Interview for Cognitive Status; MCI: mild cognitive impairment

aged 65 and older have shown that coffee consumption, but not tea drinking, was associated with a reduced risk of AD in a 5-year follow-up (65). There are some possible explanations for these conflicting results of population-based studies from the same country. Approximately one-quarter of the subjects in the MSHA also participated in the CSHA. The MSHA sample was drawn from across the province of Manitoba and included mainly rural farming locations and villages unlike the CSHA sample, which was restricted in Manitoba to two urban centers. The CSHA, a nationwide population-based cohort study, reported results of incident AD cases after well-established criteria for case identification. The MSHA investigated mainly the occupational exposure to fumigants as a possible risk factor for AD and reported about five times risk among exposed workers. These differences in rural and urban sample and the different focus of these two studies could partly explain these contrasting results. The HAAS, with over 30.2 years of follow-up on a sample of 2,459 subjects with a mean age of 52 years at baseline, showed no effect of tea intake on the risk of incident dementia and AD (66). Similar findings were obtained from the Kame Project, with 6.3 years of follow-up on a sample of 1,838 subjects aged 65 years and older, that found that tea drinking was not associated with AD risk (67). On the contrary, the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Study, with a 21 years of follow-up on 1,409 subjects with a mean age of 50.4 years at baseline, found a decreased risk of dementia by 65% and AD by 64% with daily coffee drinking of 3–5 cups, while no effect for tea consumption on dementia/AD risk was reported (68). Finally, we described above in detail the Finnish Twin Cohort Study that did not find any association between coffee drinking in midlife and cognitive performance, MCI, or dementia in old age (55). For dementia and AD prevention, a first meta-analysis of only four studies published up to January 2004 (62–65) suggested that coffee consumption was inversely associated with the risk of AD with a pooled risk estimate of 0.73 (95% CI: 0.58–0.92), despite important heterogeneity in methods and results (33). More recently, Santos and colleagues in their systematic review and meta-analysis confirmed substantially this finding suggesting for the association between caffeine intake and different measures of cognitive impairment/decline a summary significant RR of 0.84 (95% CI: 0.72–0.99), with moderate heterogeneity (34). However, in the same meta-analysis (34), the summary nonsignificant RR were 0.83 (95%CI: 0.32–2.15) for caffeine and AD, although it combines estimates from 2 case-control and 2 cohort studies, and 0.98 (95% CI: 0.87–1.11) for caffeine and cognitive decline, but results are driven predominantly by a single large study (54).

Neuroprotective effect of coffee, tea, and caffeine consumption

Different potential mechanisms can be hypothesized in explaining the neuroprotective effects against cognitive impairment/decline of coffee, tea, and caffeine consumption.

Caffeine is present in coffee, tea, soft drinks, energy drinks, and chocolate, and may enhance information processing speed, reaction time, and attention in humans (29), displaying affinities for several kinds of receptors present in the synaptic membranes, and also for cytoplasmic phosphodiesterases, enabling the modification of synaptic mechanisms (29). Most of the biological effects of caffeine, including those on the brain and the central nervous system, are mediated through antagonism of the adenosine receptors, specifically the A1 and A2A receptors (70). In fact, the long-term neuroprotective effect of caffeine may involve competitive antagonism of excessive activation of adenosine A2A receptors in the hippocampus and cortex, which may attenuate damage caused by A β (71, 72), the toxic peptide accumulating in AD brains, and might influence the synaptic transmission, so allowing the normalization of synaptic plasticity (73). Experimental findings from animal models have also shown that adenosine A2A and glutamate mGlu5R receptors are co-located, and that the former play a permissive role in mGlu5R receptor-mediated potentiation of Nmethyl-D-aspartate (NMDA) effects in the hippocampus (74). Furthermore, administration of A2A agonists may cause paradoxical effects on memory performance in the rats (75–77), suggesting that an adequate adenosinergic tonus is required for normal memory performance and that over- or down-activation of adenosine system may result in impaired memory functioning (78). Accordingly, moderate doses of caffeine improve memory performance in rodents, whereas higher doses of caffeine may impair memory acquisition (78).

Moreover, both acute or long-term caffeine administration were shown to reduce brain A β levels in AD transgenic mice (35, 36) and memory restoration and reversal of AD pathology in mice with pre-existing A β burden (79). These protective effects of caffeine across multiple cognitive domains were likely induced by caffeine's profound ability to suppress both β - and γ -secretase, resulting in decreased A β production and much lower brain A β levels/deposition (36, 79). Other complementary mechanisms of caffeine action that could contribute to its cognitive benefits in AD mice are: the ability of caffeine to decrease hippocampal levels of pro-inflammatory cytokines [e.g., tumor necrosis factor- α , interleukin (IL)-12(p70), and interferon- γ] (35); caffeine's beneficial effects on signal transduction factors involved in neuronal plasticity and survival (80); and the ability of caffeine to enhance brain mitochondrial function (81). In fact, the case-control study detailed above on plasma caffeine levels and MCI and its progression to dementia also found that 3 cytokines, granulocyte colony-stimulating factors (G-CSF), IL-10, and IL-6, were lower in the plasma of patients with MCI who were destined for AD conversion than in both the non-converting MCI participants and the participants with dementia (61). In addition, a recent study on AD transgenic mice demonstrated that caffeine could synergize with another component in coffee to enhance plasma levels of G-CSF, resulting in multiple

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Table 3

Overview of the epidemiological evidence linking coffee, tea, and caffeine consumption or plasma caffeine levels to late-life cognitive impairment/decline, mild cognitive impairment (MCI), and dementia and Alzheimer's disease (AD)

Association	References	Summary of the epidemiological evidence
Coffee, tea, or caffeine intake and late-life cognitive impairment	Jarvis 1993 (41) The Health and Lifestyle survey Johnson-Kozlow et al., 2002 (42) The Rancho Bernardo Study Kuriyama et al., 2006 (43) The Tsurugaya Project Ng et al., 2008 (44) The Singapore Longitudinal Ageing Studies Chin et al., 2008 (45) The Dublin Healthy Ageing Study Nurk et al., 2009 (46) The Hordaland Health Study Huang et al., 2009 (47) Project of Longevity and Aging in Dujiangyan Corley et al., 2010 (48) The Lothian Birth Cohort 1936 Study Wu et al., 2011 (49) 2005 National Health Interview Survey Valls-Pedret et al., 2012 (50) PREvencion con Dieta MEDiterranea (PREDIMED) study	The consumption of coffee, tea, and caffeine appeared to be associated with better cognitive test scores and a lower risk for late-life cognitive impairment
Coffee, tea, or caffeine intake and MCI	Laitala et al., 2009 (55) The Finnish Twin Cohort Study Cao et al., 2012 (61) Multisite study from the Miami and Tampa areas Lammi et al., 1989 (51)	The findings on the association of coffee, tea, and caffeine consumption or plasma caffeine levels with incident MCI and its progression to dementia were too limited to draw any conclusion
Coffee, tea, or caffeine intake and late-life cognitive decline	Several studies suggested that coffee, tea, and caffeine consumption may be linked to the decreased risk of developing late-life cognitive decline Finnish cohort of the Seven Countries Study and other Finnish cohorts van Boxtel et al., 2003 (52) The Maastricht Aging Study van Gelder et al., 2007 (53) The Finland, Italy, and The Netherlands Elderly Study Ritchie et al., 2007 (54) The Three City Study Ng et al., 2008 (44) The Singapore Longitudinal Ageing Studies Laitala et al., 2009 (55) The Finnish Twin Cohort Study Santos et al., 2010 (56) Arab et al., 2011 (57) The Cardiovascular Health Study Gelber et al., 2011 (58) The Honolulu-Asia Aging Study Feng et al., 2012 (59) The Chinese Longitudinal Healthy Longevity Survey Vercambre et al., 2013 (60)	
Coffee, tea, or caffeine intake and dementia and AD	The Women's Antioxidant Cardiovascular Study Broe 1990 (62) Maia and de Mendonça, 2002 (63) Tyas et al., 2001 (64) The Manitoba Study of Health and Aging Lindsay et al., 2002 (65) The Canadian Study of Health and Aging Laurin et al., 2004 (66) The Honolulu-Asia Aging Study Dai et al., 2006 (67) The Kame Project Eskelinen et al., 2009 (68) The Cardiovascular Risk Factors, Aging and Dementia Study Laitala et al., 2009 (55) The Finnish Twin Cohort Study Gelber et al., 2011 (58) The Honolulu-Asia Aging Study Cao et al., 2012 (61) Multisite study from the Miami and Tampa areas	Population-based studies with baseline examination in midlife pointed to a lack of association, but other case-control and longitudinal population-based studies with a briefer follow-up supported a protective effect of coffee, tea, and caffeine consumption or plasma caffeine levels against dementia and AD

therapeutic actions against AD (82). Furthermore, long-term caffeine administration (over months) improved cognitive abilities, reduced A β levels, and stimulated cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA) activity in the hippocampus of mice expressing human APP transgene with the Swedish mutation (APP^{swe}) (36, 79). In particular, with a two-week treatment with caffeine, the striatum of APP^{swe} mice exhibited changes in the expression and activity of key signaling factors whose activities are affected by AD pathology (80). Specifically, an increase in the levels of phospho-extracellular signal-regulated kinase (ERK) and phospho- c-Jun N-terminal kinases (JNK) and a decrease in the expression of phospho-cAMP response element-binding protein (CREB) was observed (80). More significantly, the two-week treatment with caffeine decreased the expression of phospho-JNK and phospho-ERK in both striatum and cortex, as well as stimulated the activity of PKA and CREB in the striatum (80). These findings may suggest that caffeine shifts the balance between neurodegeneration and neuronal survival toward the stimulation of pro-survival cascades and inhibition of pro-apoptotic pathways in the striatum and/or cortex, which may contribute to its beneficial effects against AD (80). Finally, a study in APP^{swe} transgenic mouse and cell models of AD demonstrated that caffeine and increased cyclic nucleotide levels likely block melatonin signaling to mitochondria by independent mechanisms that do not involve adenosine receptor antagonism, increasing mitochondrial function (81).

Biological effects of caffeine on brain function included modulation of white matter lesions (WMLs) and/or microvascular ischemic lesions (83), this observation was dose-dependent, so providing further evidence of coherence. Among biological hypotheses linking caffeine use and WMLs, adenosine-associated decreases in BBB permeability (39) may reduce the amount of A β passing into the brain. Furthermore, WMLs may be linked to both clinical and silent stroke, and changes in extracellular adenosine during ischemia may provide a neuroprotective response. Moreover, chronic caffeine administration has shown to have neuroprotective effects in the experimental models of hypoxia and ischemia, also related to caffeine action as adenosine receptor antagonist (84). Caffeine use also improved insulin sensitivity (85), so reducing the risk of type 2 diabetes (86), which is a strong risk factor for cognitive decline. In fact, coffee/caffeine consumption is associated with a decreased risk of type 2 diabetes and possibly also with a decreased dementia risk (86). Another proposed mechanism for explaining these associations is that magnesium that is abundant in coffee would increase insulin sensitivity (87). Moreover, caffeine could in part compensate the cognitive decline in older individuals because its effects on vigilance and attention, mainly in situations of reduced alertness (88). Habitual and moderate consumption of coffee may prevent MCI through attenuation of subclinical neuroinflammation (89), and reduction in oxidative stress (90). More generally, protective effects of caffeine in cognitive aging could also be

mediated through benefits on psychological factors, as caffeine may improve depressive symptoms (91), which, in turn, may protect against decline in cognitive functioning (92). Finally, caffeine half-life is reduced in smokers (93), which may contribute to a weaker protective effect in tobacco consumers. Furthermore, smoking is associated with coffee consumption, the latter effect is more likely in men, among whom the prevalence of tobacco consumption tends to be higher (94), in accordance with the observation of a stronger protective effect of caffeine in women by some authors (44, 54, 56, 76). This gender-related effect could involve also differences in caffeine metabolism or in sensitivity to the pharmacologic effect, as well as hormonal factors.

Beyond the neuroprotective effects of caffeine, coffee is also a source of many other constituents that may contribute to its biological activity, including, for example, potassium, niacin, magnesium, and antioxidant substances, such as tocopherols and polyphenol chlorogenic acid (the ester of caffeic acid and quinic acid) (95, 96). This polyphenol, particularly abundant in coffee, is probably responsible for a major part of coffee antioxidants (97). Additionally, the diterpenes cafestol and kahweol are natural constituents of coffee beans, and have been associated with an increased risk of high serum total and low density lipoprotein (LDL) cholesterol concentrations in some observational studies (98). However, these diterpenes are mostly removed from coffee by filtering, so modulating the cholesterol-raising effect of coffee (96). At present, there is a renowned role of vascular risk factors for the development of dementia and AD (13), while the role of coffee on vascular risk factors and outcomes is still unclear (99). Unfiltered coffee increases cholesterol levels, but caffeine might have a positive effect on serum lipids (100). Moreover, also in tea other substances different from caffeine might also affect cognition in man, such as theanine that crosses the BBB and is present in tea and mushroom (40, 101). Polyphenols, particularly flavonoids like catechins (flavan-3-ols), constitute the most interesting group of green tea leaf components (102, 103). Green tea contains more catechins than black tea or oolong tea, and these substances are *in vitro* and *in vivo* strong antioxidants. In addition, the content of certain minerals and vitamins increases the antioxidant potential of this type of tea.

Conclusions

Epidemiological reports and experimental studies based on animal and cell AD models suggested a protective role of coffee, tea, and caffeine consumption against late-life cognitive impairment/decline or dementia and AD. Caffeine intake was related to a reduction of risk of different measures of cognitive impairment/decline (34). For all studies of tea and most studies of coffee and caffeine, the estimates of cognitive decline were lower among consumers (69) (Table 3), although there was a lack of a distinct dose-response association, with a stronger effect among women than men (69). In particular, several

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cross-sectional (41-50) and longitudinal (44, 51-61) population-based studies suggested a protective effect of coffee, tea, or caffeine use against cognitive impairment/decline, although, the association was not found in all cognitive domains investigated (Table 3). The findings on the association of coffee, tea, and caffeine consumption or plasma caffeine levels with incident MCI and its progression to dementia were too limited to draw any conclusion (55, 61) (Table 3). For dementia prevention, a reduced risk of dementia and AD with moderate daily coffee consumption in midlife was reported (68), although other studies with baseline examination in midlife pointed to a lack of association (55, 58, 66). However, other case-control (63) and longitudinal population-based studies with briefer follow-up periods (65) supported favourable effects of coffee consumption also against AD (Table 3).

Therefore, taken together these findings indicated that moderate coffee, tea, and caffeine intake may decrease the risk of cognitive impairment/decline and dementia/AD later in life, which might have important implications for the prevention or delaying the onset of these age-related disorders. In fact, very recent findings showed that tea consumption may be cross-sectionally associated also with better physical functional performances in community-living older adults (104), so suggesting a possible role also in disability-related conditions in older age such as frailty syndrome. In a randomized controlled trial, a combination of green tea extract and L-theanine has been reported to have beneficial effects on cognition improving memory and attention in MCI subjects (105), and suggesting a potential of this combination as an intervention for cognitive improvement. It is unclear if the effect of coffee or tea consumption may be mediated only by the caffeine or by other bioactive components of these beverages, or due to characteristics of consumers compared with nonconsumers. However, many questions remain for future research, addressing for example possible confounders. The population-based studies may suffer from a lack of attention to item response bias in the measures of cognition, and reliance on self-report for data on coffee/tea drinking may constitute another limitation. Differences in ranges of intakes may prohibit direct comparisons with doses of coffee, tea, and total caffeine intakes estimated across studies. In fact, the content of caffeine per cup varies largely according to the serving size (50–190 ml), the preparation method (boiled, filtered, percolated, espresso, instant), and the type of the coffee used (Arabica or Robusta), with 71–220 mg caffeine/150 ml for coffee and 32–42 mg caffeine /150 ml for tea (106) (Tables 1 and 2). Moreover, caffeine may be also underestimated for the questionnaires used because some caffeinated sources (sodas or chocolate) may be not added to the total weekly caffeine consumption. However, measurement error is inevitable for dietary exposures, and older individuals may poorly remember their usual consumption of foods and beverages, and this may be particularly true for studies on cognitive impairment/decline. Several of the cross sectional and longitudinal analyses of the

studies reviewed were adjusted for several confounding factors (Tables 1 and 2), but it is not possible to completely exclude the potential effect of unmeasured confounders and residual confounding. Moderate coffee or tea drinking may be related for example with otherwise healthy and social lifestyle that may confer part of the protective effects or some medical conditions may be overrepresented and may negatively affect cognitive functions. Persons drinking larger amounts of coffee may have higher total and LDL cholesterol values and may be more often smokers than persons drinking less coffee, we cannot totally exclude some residual confounding. Further studies are needed to investigate possible dose-response effects and also effect modification by gender, apolipoprotein E (APOE) genotype, and other lifestyle and vascular factors. In particular, for APOE polymorphism, only three studies analyzed the potential effect of APOE gene on the association between coffee, tea, and caffeine use and cognitive decline/dementia (56, 69, 78). In the SLAS, the negative association between tea consumption and cognitive decline in the category defined as “high intake” did not change meaningfully after adjustment for APOE $\epsilon 4$ allele carrier status (56). In the CAIDE Study, the results obtained through stratification according to the APOE $\epsilon 4$ allele carrier status suggested a stronger protective effect of moderate coffee consumption in APOE $\epsilon 4$ allele carriers (78). Finally, in the HAAS, although there were no significant associations between coffee or caffeine intake and risk of cognitive impairment, overall dementia, AD, VaD, or moderate/high levels of the individual neuropathologic lesion types, men in the highest quartile of caffeine intake (>277.5 mg/d) were less likely than men in the lowest quartile (≤ 115.5 mg) to have any of the lesion types after adjustment for APOE $\epsilon 4$ status, smoking, physical activity, elevated total cholesterol, and history of hypertension (69). Among lifestyle factors, in several cross-sectional and longitudinal studies, alcohol consumption was one of the potential confounding factors for the association between coffee, tea, and caffeine use and late-life cognitive impairment/ decline (41, 44, 45, 52, 53, 56, 58, 60) or dementia/AD (58, 63, 67). In fact, higher coffee and tea consumption were associated with higher alcohol consumption (41, 60) or elevated proportions of alcohol drinkers (44). On the other hand, alcohol use was positively correlated with global cognitive performance together with tea intake (45), or the effect of alcohol was absent (52, 63). Finally, in the CHS, alcohol showed a weak positive trend with coffee consumption in men, but addition of the alcohol covariate to multivariable models had no appreciable effect on the beverage estimates (57).

Answers to these questions will help us to better define the target populations for future preventive and therapeutic strategies. Hopefully, in the future, further prospective studies evaluating the association between coffee, tea, and caffeine consumption and cognitive decline/dementia are needed, addressing other potential bias and confounding sources. In fact, consensual criteria for the definition of outcome as well

as creating defined categories and types of exposure might be useful in conducting epidemiological studies for the detection of these associations. Also the relation between duration of exposure to caffeine and dementia or cognitive decline and the change in caffeine intake habits over time are a source of heterogeneity across studies and should be addressed in future studies. Furthermore, also repeated measures of coffee, tea, and caffeine use would be used to characterize older individuals because baseline values are useful only if there is a relative stability in consumption over time. Finally, also more sensitive outcomes such as findings from neuroimaging studies should become available from experimental data, so further explaining the mechanisms underlying the neuroprotective effects of coffee, tea, and caffeine consumption.

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