Associations Between Caffeine Consumption, Cognitive Decline, and Dementia: A Systematic Review

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Accepted 21 September 2020

Abstract

Background: Epidemiologic studies have provided inconclusive evidence for a protective effect of caffeine consumption on risk of dementia and cognitive decline.

Objective: To summarize literature on the association between caffeine and 1) the risk of dementia and/or cognitive decline, and 2) cognitive performance in individuals with mild cognitive impairment (MCI) or dementia, and 3) to examine the effect of study characteristics by categorizing studies based on caffeine source, quantity and other possible confounders.

Methods: We performed a systematic review of caffeine effects by assessing overall study outcomes; positive, negative or no effect. Our literature search identified 61 eligible studies performed between 1990 and 2020.

Results: For studies analyzing the association between caffeine and the risk of dementia and/or cognitive decline, 16/57 (28%) studies including a total of 40,707/153,070 (27%) subjects reported positive study outcomes, and 30/57 (53%) studies including 71,219/153,070 (47%) subjects showed positive results that were dependent on study characteristics. Caffeine effects were more often positive when consumed in moderate quantities (100–400 mg/d), consumed in coffee or green tea, and in women. Furthermore, four studies evaluated the relationship between caffeine consumption and cognitive function in cognitively impaired individuals and the majority (3/4 [75%]) of studies including 272/289 subjects (94%) reported positive outcomes.

Conclusion: This review suggests that caffeine consumption, especially moderate quantities consumed through coffee or green tea and in women, may reduce the risk of dementia and cognitive decline, and may ameliorate cognitive decline in cognitively impaired individuals.

Keywords: Caffeine, coffee, cognition, dementia, review, tea

INTRODUCTION

Dementia is a clinical syndrome characterized by progressive deterioration of cognitive functions and loss of independence in activities of daily living. Approximately 50 million people are living with dementia worldwide. This number is continuously rising [1], and in 2017 the World Health Organization listed dementia as a public health priority [2]. A range of neuropathological disease entities may underlie a dementia syndrome, including Alzheimer’s disease (AD), vascular pathology (VaD), Lewy bodies (DLB), Parkinson’s disease (PD), or frontotemporal lobar degeneration [1]. Many factors such as cardio- and cerebrovascular disease, metabolism, psychiatric conditions, lifestyle, and education, potentially contribute to the risk of different types of dementia [3]. Furthermore, recent studies have suggested endo- and neurocrine interactions between gut microbiota and

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the brain (i.e., the microbiota-gut-brain axis [4, 5]) and that dietary factors such as caffeine intake can thereby influence the risk of dementia [6].

Caffeine is a psychoactive substance that is present in many beverages and some foods. The most widely known and consumed caffeine source is coffee, but caffeine can also be found in tea, energy drinks, carbonated soft drinks, fruits, and cocoa-containing foods [7, 8]. After caffeine ingestion the substance is absorbed into the bloodstream via the gastrointestinal tract. From there, caffeine is distributed throughout the entire body. Caffeine biologically acts as an adenosine A1 and A2A receptor antagonist, and these receptors are widely distributed throughout the central and peripheral nervous system [9]. By blocking adenosine receptors, caffeine is capable of exerting effects on metabolism, the cardiovascular system, the respiratory system, and neuroinflammatory, neuro-modulatory, and neuroprotective processes [10, 11]. More specifically, caffeine may stimulate gastric acid secretion and vasoconstriction, elevate the heart rate and blood pressure, increase the respiratory rate, and ultimately decrease neurodegeneration. Caffeine is able to enhance alertness, wakefulness, psychomotor vigilance, and memory, possibly also through an effect on NMDA receptors [12–14]. Furthermore, caffeine may reduce neuroinflammation and afford neuroprotection, through the consecutive lowering of extracellular calcium, glutamate release from the cell, and microglial activation [15]. There are also health risks associated with excessive caffeine consumption, including anxiety, panic attacks, psychosis, mania, tension, nervousness, irritability, restlessness, nausea, palpitations, insomnia, and diuresis [16].

Research in animal models indicates that caffeine can ameliorate cognitive decline [17]. Studies assessing possible mechanisms underlying this effect have suggested that the effects of caffeine on A2A receptors can control abnormal synaptic plasticity and synaptic toxicity [18, 19]. Other studies have posited that caffeine intake may delay or reduce the risk of AD by decreasing hippocampal amyloid-β levels in transgenic mice through A2A receptor blockade [20, 21].

In human epidemiological studies, results for the protective effects of caffeine on cognitive decline and dementia have been mixed. Some studies suggest positive influences of caffeine intake on neurological disorders and dementia [22, 23], while other studies have found no associations between caffeine and dementia [24, 25]. The association between caffeine consumption, cognitive decline, and dementia therefore remains inconclusive.

Here, we summarize the available literature on this topic and provide a systematic review. We aimed to address whether there is an association between caffeine and 1) the risk of dementia and/or cognitive decline, and 2) cognitive function in already cognitively impaired individuals (i.e., MCI or dementia). We further aimed to examine the effects of study characteristics (e.g., caffeine source and quantity) and demographic variables of the study sample (e.g., age and sex) on study outcomes.

METHODS

Study selection procedure

We searched the PubMed and Web of Science databases for studies published before June 2, 2020, using the following (combination of) search terms: ‘caffeine’, ‘coffee’, ‘tea’, AND ‘dementia’ OR ‘Alzheimer’s’, AND ‘cognitive’ or ‘cognition’. Only peer-reviewed articles on studies in humans that were published in English, were eligible for inclusion in this pre-determined systematic review. Cross references were additionally assessed for eligibility. We included cognitively unimpaired individuals as well as individuals diagnosed with any type of dementia and/or MCI. The main criteria for article selection were 1) provision of information on the relation between caffeine consumption and the risk of dementia/cognitive decline, and/or 2) assessment of the association of caffeine on cognitive function in individuals with mild cognitive impairment (MCI) or dementia. Because many studies included a mixed sample of persons with dementia and MCI, both groups were taken together and termed ‘cognitively impaired’ subjects. We included any paper that described original research, regardless of study design, and, therefore, cross-sectional, longitudinal, case-control, controlled trials, cohort, and pilot studies were all assessed in the present review.

Risk of bias assessment

This review was performed according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement (Supplementary Table 1) [26]. The risk of bias for each study was assessed using the Cochrane Collaboration’s tool for non-randomized studies for interventions (ROBINS-I) [27]. Several risk of bias domains were evaluated for each study, including bias due to confounding factors, subject selection, classification of intervention, deviation from intended intervention, missing data,
outcome measurement and reporting of results. Each domain was rated as ‘low’, ‘moderate’, ‘serious’, or ‘critical’ risk of bias. An overall risk of bias was derived from the quality assessment across all domains of the remaining studies. These judgments were performed independently by two authors (A.C. and C.G.) and final assessment was determined by consensus. Our analyses were confined to studies with low and moderate risk of bias, as studies with serious or critical risk of bias were excluded from the analyses.

Data analysis

Relevant data from the included studies were extracted in piloted forms. Outcome measures in the primary examination were based on overall study outcomes regarding the association between caffeine and 1) the risk of dementia and/or cognitive decline and 2) cognitive function in cognitively impaired individuals. Secondary analyses included examination of the effects of caffeine source (coffee, tea, pure caffeine, or multiple caffeine containing sources), and quantity (frequency and dosage), and possible confounders (e.g., age or sex), on study outcomes. Based on a previous study [28], the quantity of caffeine consumption was divided into three categories: low (<100 mg/d), moderate (100–400 mg/d), and high caffeine consumption (>400 mg/d). In accordance with the concentrations of caffeine across sources (i.e., 71–220 mg caffeine/150 ml for coffee and 32–42 mg caffeine/150 ml for tea [29]), moderate caffeine consumption will be defined as 1–4 cups of coffee or 3–10 cups of tea per day. Low caffeine consumption will be defined as <1 cup of coffee or <3 cups of tea per day, and high caffeine consumption will be defined as >4 cups of coffee or >10 cups of tea per day. Outcomes were defined as positive (caffeine improved cognition or slowed down cognitive decline), negative (negative association with cognition), or no association (no relation between caffeine and cognition). Study outcomes could also be mixed, for instance when positive effects were only found in a subset of the sample or when study outcomes were dependent on study characteristics, like caffeine source used.

RESULTS

Study selection and characteristics

The identification of relevant studies is illustrated in a flow diagram (Fig. 1). Through database searches on PubMed, Web of Science, and cross references, we identified a total of 629 records. First, we excluded 522 articles, including 160 duplicates, based on review of the title and abstract. After full-text assessment of the remaining 107 articles, we excluded 44 articles that had highly overlapping study populations (n = 7), incompatible study designs (n = 4), no suitable cognitive outcome measures (n = 12), only non-caffeine effects (n = 11), or combined interventions (n = 10) (Supplementary Table 2). The remaining 63 studies were assessed for risk of bias, which resulted in the exclusion of two studies [30, 31] (see “Risk of bias” section). The final selection (61 studies) comprised 48 cohort studies, nine case-control studies, three randomized controlled trials, and one pilot study.

The included studies were published between 1990 and 2020, and were executed in 24 different countries (Table 1): United States of America (n = 10) [24, 25, 32–39], Japan (n = 9) [40–48], China (n = 8) [49–56], United Kingdom (n = 4) [57–60], Finland (n = 3) [28, 61, 62], The Netherlands (n = 4) [62–65], Taipei (n = 3) [66–68], Canada (n = 2) [69, 70], France (n = 2) [71, 72], Portugal (n = 2) [73, 74], Singapore (n = 2) [75, 76], Italy (n = 2) [62, 77], Australia (n = 1) [78], Brazil (n = 1) [79], Germany (n = 1) [80], Iran (n = 1) [81], Ireland (n = 1) [82], Jordan (n = 1) [83], Norway (n = 1) [84], Scotland (n = 1) [85], South Korea (n = 1) [22], Spain (n = 1) [23], Sweden (n = 1) [86], and Switzerland (n = 1) [87]. One study [62] was performed in a multi-national collaboration between Finland, Italy, and the Netherlands. The final selection of articles comprised a total of 153,359 subjects (excluding subjects in the control group), which were either cognitively impaired (AD, DLB, PD, VaD, MCI, or undefined dementia) or cognitively unimpaired.

Risk of bias

Using the Cochrane Collaboration tool, an assessment of bias was performed for all included studies, which lead to the exclusion of two studies [30, 31] (Supplementary Table 3). Furthermore, 39/61 studies had low risk of bias and 22/61 studies had moderate risk of bias. Assessment of bias across risk of bias domains revealed predominantly moderate- to low risk of bias for six out of seven domains (Fig. 2). High risk of bias was observed on the ‘deviations from intended interventions’ domain, which could be explained by most studies employing self-reported data.
Associations between caffeine consumption and cognition

Caffeine and the risk of dementia/cognitive decline

Of the 61 articles included in this review, 57 studies with a total of 153,070 subjects, assessed the association between caffeine and the risk of dementia and/or cognitive decline (Fig. 3A, B). Within these studies, 16/57 (28%) studies including 40,707/153,070 (27%) subjects found a positive association for caffeine on the risk of dementia and/or cognitive decline that was independent of study related factors. Approximately half of the studies (30/57 (53%) studies including 71,219/153,070 (47%) subjects) reported positive results that were dependent on caffeine consumption quantity \((n=14)\), type of caffeine source \((n=11)\), sex \((n=7)\), age \((n=4)\), caffeine consumption duration (short- or long-term effects) \((n=2)\), and/or adjustments for covariates \((n=3)\). No association between caffeine and risk of dementia or cognitive decline was found in 11/57 (19%) studies including 41,144/153,070 (27%) subjects.

Caffeine and cognitive function in cognitively impaired individuals

Four studies [22, 35, 40, 41] with a total of 289 subjects assessed the influence of caffeine consumption on cognitive function in cognitively impaired individuals. Cao et al. (2012) [35] assessed concurrent plasma caffeine levels in MCI subjects over a time period of 2–4 years, and observed a reduction in progression to dementia at plasma caffeine levels >1200 ng/ml in this population. Cho et al. (2018) [22] found better global cognitive scores for individuals with PD that consumed coffee, compared to their non-coffee consuming counterparts. Ide et al. (2014) [40] and Ide et al. (2016) [41] both assessed cognitively impaired individuals with AD, VaD, or DLB that consumed green tea powder over a time
Table 1
Characteristics of studies included in the review (n = 61)

| Study | Study design/cohort | Cohort | Subjects (N and population) | Control (N and population) | Selected cognition measure/domain | Age (y) | Sex (% men) | Caffeine source consumption/retrospective/prospective assessed | Effect and principle findings (Positive effect+, negative effect-, no effect/HR, OR or RR (95% CI), or p-value) |
|-------|---------------------|--------|-----------------------------|-----------------------------|-------------------------------|---------|-------------|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| 1. Al-khateeb et al. 2014 [83] Jordan | Cross-sectional case-control study | Senior homes and Jordan University Hospital | 52 dementia | 50 cognitively healthy | MMSE | 69.8 (7.4) | 61% | Coffee +, protective effect of coffee against cognitive decline, with a 6.25-fold lower risk with increased intake. OR = 0.16 (0.066–0.37) |
| 2. Arab et al. 2011 [32] USA | Longitudinal cohort study prospective median: 7.9 y | The Cardiovascular Health Study (CHS) | X/4,809 subjects, caffeine consumer | X/4,809 subjects, non-caffeine consumer | 3MSE | 72.6 (5.4) | 43% | Coffee, Tea (NS) prospective +, association coffee and tea consumption with reduced rates of cognitive decline in women. Tea: p = 0.007, Coffee: p = 0.02, no association in men. Tea: p = 0.67, Coffee: p = 0.99 |
| 3. Araújo et al. 2015 [79] Brazil | Cross-sectional cohort study retrospective 12 mo | The Longitudinal Study of Adult Health (ELSA-Brasil) | 13,165 subjects, coffee consumer | 1,398 subjects, non-/low coffee consumer | Learning, recall, and word recognition tests | 52.0 (9.0) | 46% | Coffee retrospective +, moderate coffee consumption (2–3 cups/d) associated with better cognitive function in elderly only (65–74 y). p = 0.025 /, no association for low and high coffee consumption, and for adults (35–64 y). +, higher coffee consumption (≥ 3 cups/d) associated with better cognitive performance. p = 0.026 /, no association in a longitudinal model. |
| 4. Araújo et al. 2016 [63] The Netherlands | Longitudinal and cross-sectional cohort study prospective 5.5 y | The Rotterdam Study 2005–2009 | 2,914 subjects | NA | LDST | 59.3 (7.2) | 45% | Coffee retrospective +, higher coffee consumption (≥ 3 cups/d) associated with better cognitive performance. p = 0.026 /, no association in a longitudinal model. |
| 5. Beydoun et al. 2014 [33] USA | Longitudinal and cross-sectional cohort study prospective 46 y | The Baltimore Longitudinal Study of Aging (BLSA) | 3,047 subjects, follow-up | 3,047 subjects, baseline | MMSE | 58.9 (18.0) | 60% | Multiple sources (NS) prospective +, association coffee intake with better global cognitive function at baseline for age >70 y. p = 0.008 /, no association found for age <70 y. |

(Continued)
| Study | Study design/ prospective / length of follow-up | Cohort | Subjects (N and population) | Control (N and population) | Selected cognition measure/ domain | Age (y) | Sex (% men) | Caffeine source consumption/ effect and principle | Effect and principle findings (Positive effect+, negative effect -, no effect/) | p-value |
|-------|-----------------------------------------------|--------|-----------------------------|-----------------------------|----------------------------------|--------|-------------|-----------------------------------------------|-----------------------------------------------|---------|
| 6. Boot et al. 2013 [34] USA | Cross-sectional case-control study retrospective NA | The Mayo Clinic Study of Aging; The Alzheimer Disease Patient Registry; Alzheimer Disease Research Center Study | 383 cognitively impaired (236 AD, 147 DLB) | 294 cognitively healthy | NA | 82.4 (7.5) | 63% | Multiple sources (coffee, tea and caffeinated soda) | +, association caffeine intake and reduced risk of DLB. OR = 0.29 (0.14–0.57) retrospective | |
| 7. Broe et al. 1990 [78] Australia | Cross-sectional case-control study retrospective NA | The Repatriation General Hospital Concord and Lidcombe Hospital | 170 AD | 170 cognitively healthy | MMSE | 78.1 (7.3) | 38% | Coffee, Tea (NS) | /, no association between tea and coffee consumption and reduced risk of AD. Tea: OR = 2.25 (0.72–7.71) Coffee: OR = 2.25 (0.72–7.71) | |
| 8. Chen et al. 2012 [49] China | Longitudinal case-control study prospective 3 y | The Chinese Longitudinal Health Longevity Study (CLHLS) 2002 | 1306 cognitive decline | 4385 cognitive healthy | MMSE (Chinese version) | 82.9 (11.0) | 24% | Tea (NS) | +, association tea drinking with cognitive decline. p = 0.0468 | |
| 9. Chin et al. 2008 [82] Ireland | Cross-sectional cohort study retrospective NA | The Dublin Healthy Ageing Study | 466 cognitively healthy | NA | MMSE | 75.5 (6.1) | 45% | Tea (NS) | +, tea intake positively correlated with global cognitive performance. p = 0.042 | |
| 10. Chuang et al. 2019 [66] Taipei | Longitudinal and cross-sectional cohort study prospective 11 y | The Nutrition and Health Survey in Taiwan (NAHSIT) 2014–2016 and 1999–2000 | 516 subjects, caffeine consumer | 912 subjects, non-flow caffeine consumer | SPMSQs and MMSE (Chinese version) | 73.6 (0.8) | 51% | Coffee, Tea (NS) | +, higher intake (moderate consumption: ≥ 7 times/wk) of tea and coffee associated with lower risk of dementia Coffee: OR = 0.55 (0.30–0.98) Tea: 0.46 (0.28–0.78) /, no association with low coffee and tea consumption, and in men only. | |
| 11. Corley et al. 2010 [85] Scotland | Cross-sectional, cohort study retrospective 2–3 mo | The Lothian Birth Cohort 1936 Study; The Scottish Mental Survey 1947 | 893 subjects | NA | Memory | 69.5 (0.8) | 48% | Multiple sources (14 caffeine-containing items, e.g., coffee, tea, chocolate, etc.) | +, general cognitive ability and memory with adjustments for age and sex. p = 0.02 /, no association with cognitive function when additionally adjusted for occupational social class and childhood IQ. p = 0.11 | |
| Study | Type | Subjects | Coffee Consumption | Cognitive Outcome | Methodology | Risk | Significant |
|-------|------|----------|--------------------|------------------|-------------|------|-------------|
| Dai et al. 2006 [36] USA | Longitudinal cohort study prospective 6.3 y | The KAME Project | 1,275 subjects, tea consumer | 315 subjects, non-flow tea consumer | CASI | 71.8 | 46% Tea (NS) retrospective |
| Dong et al. 2020 [50] China | Longitudinal cross-sectional cohort study retrospective 24 h | National Health and Nutrition Examination Survey (NHANES) 2011–2014 | 1,803 subjects, coffee consumer | 710 subjects, non-coffee consumer | DSST | NA; >60 y | Coffee retrospective |
| Driscoll et al. 2016 [37] USA | Longitudinal and cross-sectional cohort study prospective 10 y | Women’s Health Initiative Memory Study | 2,541 subjects, caffeine consumer | 2,926 subjects, non-low caffeine consumer | 3MSE | Range: [65–80] | Multiple sources (coffee, tea and cola) retrospective |
| Eskelinen et al. 2009 [28] Finland | Longitudinal cohort study prospective 21 y | The Cardiovascular Risk Factors, Aging and Dementia study (CAIDE) (North Karelia Project and FINMONICA study) | X/1,409 subjects, caffeine consumer | X/1,409 subjects, non-coffee consumer | MMSE | 71.3 (4.0) | Coffee, Tea (NS) retrospective |
| Feng et al. 2012 [75] Singapore | Longitudinal cohort study prospective 7 y | The Chinese Longitudinal Health Longevity Study (CLHLS) 1998 | 3,187 subjects, tea consumer | 3,952 subjects, non-tea consumer | Verbal fluency test | 91.4 (7.5) | 42.9% Tea (NS) retrospective |
| Feng et al. 2018 [25] USA | Longitudinal cohort study prospective 6.8 y | The Osteoporotic Fractures in Men (MrOS) Cohort | 1,430 subjects, tea consumer | 2,414 subjects, non-tea consumer | 3MSE | 72.4 (5.2) | 100% Tea (black tea) retrospective |
| Fischer et al. 2018 [80] Germany | Longitudinal cohort study prospective 10 y | Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe) Cohort | 2,622 subjects (2,204 cognitively healthy, 418 incident dementia), | 2,622 cognitively healthy, baseline | CERAD memory score | 81.2 (3.4) | 35% Coffee, Tea (green tea) retrospective |

(Continued)
| Study | Study design retrospective/ prospective length of follow-up | Cohort | Subjects (N and population) | Control (N and population) | Selected cognition measure/ domain | Age (y) | Sex (% men) | Caffeine source consumption retrospective/prospective (HR, OR or RR) | Effect and principle findings (Positive effect+, negative effect -, no effect) |
|-------|------------------------------------------------------------|--------|-----------------------------|-----------------------------|----------------------------------|---------|-------------|-------------------------------------------------------------|--------------------------------------------------------------------------------|
| 19. Gelber et al. 2011 [24] USA | Longitudinal case-control study prospective 25 y | The Honolulu-Asia Aging Study (HAAS) | 2,787 cognitively healthy, coffee consumer | 707 cognitively healthy, non-/low coffee consumer | CASI | 52.5 (4.5) | 100% | Coffee, Multiple sources (coffee, tea, cola) | \( \text{OR} = 1.05 (0.58–1.90) \), no association between coffee or general caffeine intake and risk of dementia and cognitive impairment. \( p = 0.99 \) |
| 20. Gu et al. 2018 [51] China | Cross-sectional case-control study retrospective NA | The Weitang Geriatric Diseases Study | 1,570 subjects (1,416 cognitively healthy, 155 cognitively impaired), habitual tea consumers | 3,008 subjects (2,218 cognitively healthy, 790 cognitively impaired), non-habitual tea consumers | AMT | 67.6 (6.3) | 48% | Tea (green and other tea types) | \( \text{OR} = 0.74 (0.56–0.99) \), no association between tea consumption and risk of cognitive impairment. \( p = 0.004 \) |
| 21. Haller et al. 2018 [87] Switzerland | Longitudinal cohort study prospective 3 y | Elderly in Geneva and Lausanne counties | 145 subjects, follow-up | 145 subjects, baseline | MMSE | 73.8 (3.5) | 44% | Coffee | \( \text{OR} = 0.45 (0.21–0.95) \), no association for low coffee consumption. \( p = 0.99 \) |
| 22. Huang et al. 2009 [52] China | Cross-sectional cohort study retrospective 2 y | The Project of Longevity and Aging in Dujiangyan (PLAD) | 429 cognitively impaired | 252 cognitively healthy | MMSE | 93.5 (3.3) | 33% | Tea (NS) | \( \text{OR} = 0.45 (0.21–0.95) \), no association for coffee consumption. \( p = 0.004 \) |
| 23. Iranpour et al. 2020 [81] Iran | Cross-sectional cohort study retrospective 24 h | National Health and Nutritional Examination Surveys (NHANES) 2013–2014 | 1,065 subjects, ≥Q2 caffeine consumer | 375 subjects, Q1 caffeine consumer | DSST | 69.8 (2.3) | 51% | Multiple sources (e.g., tea, soda, chocolate, etc.) | \( \text{OR} = 0.45 (0.21–0.95) \), no association for low coffee consumption. \( p = 0.99 \) |
| 24. Jarvis 1993 [57] UK | Cross-sectional cohort study retrospective NA | The Health and Lifestyle Survey | X/7,414 subjects, caffeine consumer | X/7,414 subjects, non-caffeine consumer | Reaction time, incidental verbal memory and visuo-spatial reasoning | NA: ~ 45 | 45% | Coffee, Tea (NS) | \( \text{OR} = 0.45 (0.21–0.95) \), no association for coffee consumption. \( p = 0.99 \) |
| Study | Design | Location | Sample Size | Cognitive Status | Measure | Mean | SD | Type | Results |
|-------|--------|----------|-------------|------------------|---------|------|----|------|---------|
| 25. Johnson-Kozlow et al. 2002 [38] USA | Cross-sectional cohort study prospective | The Rancho Bernardo Study, 1988–1992 | 1,528 cognitively healthy | NA | MMSE | 72.9 (9.0) | 42% | Coffee retrospective | +, association between higher lifetime coffee consumption and better cognitive performance in women. p = 0.023 |
| 26. Kitamura et al. 2016 [42] Japan | Cross-sectional cohort study retrospective | The Project in Sado for Total Health (PROST) 2008–2014 | 601 subjects (490 cognitively healthy, 111 cognitively impaired), tea consumer 50 cognitively healthy, 133 cognitively impaired), non-tea consumer | MMSE | 68.9 (10.6) | 55% | Tea (green tea) retrospective | +, green tea intake associated with better cognitive performance. OR = 0.73 (0.54–0.99) |
| 27. Konishi et al. 2018 [48] Japan | Cross-sectional RCT prospective | Healthy Japanese volunteers, 2016 | 833 subjects, caffeine consumer | MMSE (Japanese version) | 74.7 (4.6) | 43% | Pure caffeine prospective | +, better executive function with caffeine consumption. p = 0.03 |
| 28. Kuriyama et al. 2006 [43] Japan | Cross-sectional cohort study retrospective | The Tsurugaya Project | 833 subjects, 170 subjects, non-low caffeine consumer | SAT: executive function | Range: [22–59] | 50% | | |
| 29. Laitala et al. 2009 [61] Finland | Longitudinal cohort study prospective | Finnish Twin Cohort Study | 2606 cognitively healthy | NA | TELE | 74.4 (5.3) | 52% | Coffee retrospective | |
| 30. Larsson & Wolk 2018 [86] Sweden | Longitudinal and cross-sectional cohort study prospective | The National Research Infrastructure SIMPLER (Swedish Infrastructure for Medical Population-based Life-course Environmental Research); Swedish Mammography Cohort and the Cohort of Swedish Men | X/28,775 subjects, caffeine consumer | NA | X/28,775 subjects, non-low caffeine consumer | 83.2 (5.1) | 53% | Coffee retrospective | /, coffee consumption not associated with risk of AD. HR = 1.01 (0.86–1.18) |
| Study | Study design | Cohort | Subjects (N and population) | Control (N and population) | Selected cognition measure/ domain | Age (y) | Sex (% men) | Caffeine source consumption retrospective/prospective effect and principle findings (Positive effect+, negative effect -, no effect/) (HR, OR or RR, 95% CI, or p-value) |
|-------|-------------|--------|-----------------------------|---------------------------|----------------------------------|---------|-------------|----------------------------------------------------------------------------------|
| 31. Lee et al. 2017 [67] Taipei | Cross-sectional cohort study retrospective NA | A Nationwide Survey in Japan, 2011–2013 | X/7,964 subjects, caffeine consumer | X/7,964 subjects, non-caffeine consumer | TMSE 75.7 (6.6) | 50% | Coffee, Tea (green and other tea types) retrospective +, inverse associations with dementia. Coffee: OR = 0.59 (0.35–0.97) Green tea: OR = 0.51 (0.34–0.75) Other tea: OR = 0.41 (0.28–0.60) |
| 32. Lesk et al. 2009 [58] UK | Cross-sectional cohort study retrospective 4 h | The Oxford Project to Investigate Memory and Ageing (OPTIMA) cohort | 57 subjects, caffeine consumer | 32 subjects, non-caffeine consumer | MMSE Range: [67–95] | 38% | Multiple sources (e.g., coffee, tea, soft drinks, chocolate, etc.) retrospective |
| 33. Lindsay 2002a [69] Canada | Longitudinal case-control study prospective 5 y | The Canadian Study of Health and Aging (CSHA) | 194 AD | 3,894 cognitively healthy | MMSE Range: [69–105] | 42% | Coffee, Tea (NS) retrospective +, regular (nearly every day) coffee consumption and a reduced risk of AD. OR = 0.69 (0.50–0.96) /, no association with tea drinking. OR = 1.12 (0.78–1.61) |
| 34. Maia & de Mendonc¸a 2002 [73] Portugal | Cross-sectional, case-control study retrospective 20 y | Dementia Outpatient Clinics, Hospital Santa Maria, Lisbon | 54 AD | 54 cognitively healthy | MMSE 70.8 (7.7) | 48% | Multiple sources (e.g., coffee, tea, cola, etc.) retrospective |
| 35. Mirza et al. 2014 [64] The Netherlands | Longitudinal cohort study prospective 8.7 y | The Rotterdam Study 1989–1990 | 3,876 subjects, coffee consumer | 492 subjects, non-/low coffee consumer | MMSE NA; ~70 | 41% | Coffee retrospective +, association between coffee consumption (>3 cups/d) and incident dementia with short (0–4 y) follow-up. Short-term: HR = 0.70 (0.51–0.96) - , increased risk of incident dementia for long-term effect (>4 y), possibly due to reverse causality. Long-term: HR = 1.14 (0.83–1.56) |
| 36. Ng et al. 2008 [76] Singapore | Longitudinal and cross-sectional cohort study prospective median:16 mo | The Singapore Longitudinal Ageing Studies (SLAS) cohort | X/2,501 subjects, caffeine consumer | X/2,501 subjects, non-caffeine consumer | MMSE 66.0 (7.7) | 36% | Coffee, Tea (green and black/oolong tea) retrospective +, association regular black/oolong and green tea consumption with lower prevalence of cognitive impairment, and black/oolong tea with reduced risk of cognitive decline over time. Black/oolong: OR = 0.55 (0.40–0.76) Green tea: OR = 0.42 (0.25–0.69) /, no association for coffee. Coffee: OR = 0.99 (0.69–1.45) |
| Study | Design/Location | Participants | Exposure | Outcome | Methodology | OR (95% CI) |
|-------|----------------|-------------|----------|---------|-------------|-------------|
| J.Q. Alida Chen et al. 2014 [44] Japan | Longitudinal cohort study prospective 4.9 y | The Nakajima Project | X/490 subjects, caffeine consumer | X/490 subjects, non-caffeine consumers | MMSE 71.2 (6.4) | 33% Coffee, Tea (black and green tea) retrospective | +, reduced risk of cognitive decline with green tea. Green tea: OR = 0.53 (0.30–0.93) /, no effect for coffee or black tea on incidence of dementia or MCI. Coffee: OR = 1.22 (0.63–2.36) Black tea: OR = 1.19 (0.64–2.24) +, habitual tea intake associated with better cognitive test performance. p = 0.046 |
| Nurk et al. 2009 [84] Norway | Cross-sectional cohort study retrospective NA | The Hordaland Health Study (HUSK), Norway | 1,083 subjects, tea consumer | 948 subjects, non-tea consumer | modified MMSE Range: [70–74] | 45% Tea (NS) retrospective | +, caffeine consumption of >200 mg/d associated with reduced risk of dementia compared with caffeine consumption of <50 mg/d at age of 90. HR = 0.66 (0.43–0.99) /, no association found 20 y earlier, at age 70, or lower caffeine consumption at age 90. +, inverse association between coffee consumption (>300 mg/day) and cognitive decline in women, especially at higher ages. OR = 0.67 (0.53–0.85) /, no effect found in men. OR = 1.18 (0.87–1.59) +, caffeine intake (>62 mg/day) associated with lower risk of cognitive decline in women. RR = 0.51 (0.27–0.97) /, no effect found in men. RR = 0.51 (0.22–1.16) |
| Paganini-Hill et al. 2016 [39] USA | Longitudinal cohort study prospective 36 mo | The 90 + Study, The Leisure World Cohort Study | 587 subjects (268 incident dementia), follow-up | 587 cognitively healthy elderly, baseline | MMSE/ CASI 93 (2.6) | NA Multiple sources (e.g., coffee, black tea, green tea, soft drinks, chocolate, etc.) retrospective | +, positive association for 2–4 cups/d and > 4 cups/d tea consumption in general. 2–4 cups/d: OR = 0.71 (0.59–0.84) >4 cups/d: OR = 0.76 (0.63–0.91) /, no association for green tea and low tea consumption in general. Green tea: OR = 1.00 (0.74–1.35) <2 cups/d: OR = 1.09 (0.88–1.35) |
| Ritchie et al. 2007 [71] France | Longitudinal cohort study prospective 3.5 y | The Three-City Study (Bordeaux, Dijon, Montpellier) | 7,017 cognitively healthy, follow-up | 7,017 cognitively healthy, baseline | Isaacs 73.7 (5.2) | 40% Multiple sources (tea and coffee) retrospective | +, black tea consumption and prevalence of cognitive impairment. Black tea: OR = 0.48 (0.29–0.80) |
| Santos et al. 2010 [74] Portugal | Longitudinal cohort study prospective median: 48 mo | Elderly in Porto | 309 cognitively healthy, follow-up | 309 cognitively healthy, baseline | MMSE 70 (1.9) | 41% Multiple sources (82 caffeine-containing food items, e.g., coffee, tea, soft drinks, chocolate, etc.) retrospective | |
| Shen et al. 2015 [53] China | Cross-sectional cohort study retrospective NA | The Zhejiang Major Public Health Surveillance Program (ZPHS) 2014 | 2,530 subjects, caffeine consumer | 6,845 subjects, non-caffeine consumer | MMSE (Chinese version) 70.0 (7.7) | 48.5% Multiple sources (black, green and multiple tea types) retrospective | |

(Continued)
## Table 1
(Continued)

| Study | Study design retrospective/prospective length of follow-up | Cohort | Subjects (N and population) | Control (N and population) | Selected cognition measure/domain | Age (y) | Sex (% men) | Caffeine consumption assessment | Effect and principle findings (Positive effect+, negative effect-, no effect/) (HR, OR or RR (95% CI), or p-value) |
|-------|----------------------------------------------------------|--------|-----------------------------|----------------------------|---------------------------------|---------|-------------|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 43. Shirai et al. 2020 [45] Japan | Longitudinal cohort study prospective 5.3 y | The National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA) | X/1,305 subjects, caffeine consumer X/1,305 subjects, non-caffeine consumer | MMSE (Japanese version) | 66.7 (6.2) | 48% | Coffee, Tea (green tea) retrospective | +, association between 2–3 times/d and >4 times/d green tea consumption and reduced risk of cognitive decline. 2–3 times/d: HR = 0.71 (0.52–0.97) ≥4 times/d: HR = 0.72 (0.54–0.98) /, no association for <once/d green tea consumption and general coffee consumption in general. |
| 44. Smith 2009 [59] UK | Cross-sectional cohort study prospective NA | The Bristol Stress and Health at Work Study & The Cardiff Health and Safety and Work Study | X/3,223 subjects, caffeine consumer X/3,223 subjects, non-caffeine consumer | CFQ | 49.6 (21.9) | 43% | Multiple sources (caffeinated drinks) retrospective | +, caffeine consumption reduces risk on cognitive failures. *p* < 0.005 |
| 45. Solfrizzi et al. 2015 [77] Italy | Longitudinal cohort study prospective median: 3.5 y | The Italian Longitudinal Study on Aging (ILSA) | 985 subjects, coffee consumer 460 subjects, non-/low coffee consumer | MMSE | 71.8 (5.0) | 56% | Coffee retrospective | +, lower rate of MCI incidence for moderate (1–2 cups/d) coffee consumption. HR = 0.31 (0.13–0.75) /, no association with low coffee consumption (<1 cup/d). HR = 0.47 (0.211–1.02) -. higher rate of incidence MCI for change in coffee consumption habits. HR = 1.80 (1.11–2.92) +, coffee consumption associated with lower risk of incident dementia. HR = 0.72 (0.61–0.84) |
| 46. Sugiyama et al. 2016* [46] Japan | Longitudinal cohort study prospective 5.7 y | The Ohsaki Cohort 2006 | 11,089 subjects, caffeine consumer 2,048 subjects, non-caffeine consumer | Dementia Scale | 73.6 (5.8) | 45% | Coffee retrospective | +, Green tea consumption of >3 cups/d associated with a lower risk of incident dementia. Green tea: OR = 0.74 (0.63–0.88) /, no association found for low green tea consumption (<2 cups/d) and black and oolong tea. Green tea: OR = 0.94 (0.79–1.11) Black tea: HR = 0.98 (0.61–1.59) Oolong tea: HR = 0.89 (0.54–1.45) |
| 47. Tomata et al. 2016* [47] Japan | Longitudinal cohort study prospective 5.7 y | The Ohsaki Cohort 2006 | 11,411 subjects, caffeine consumer 2,234 subjects, non-/low caffeine consumer | CDR | 73.8 (5.8) | 44% | Tea (green, black and oolong tea) retrospective | +, Green tea consumption of >3 cups/d associated with a lower risk of incident dementia. Green tea: OR = 0.74 (0.63–0.88) /, no association found for low green tea consumption (<2 cups/d) and black and oolong tea. Green tea: OR = 0.94 (0.79–1.11) Black tea: HR = 0.98 (0.61–1.59) Oolong tea: HR = 0.89 (0.54–1.45) |
| Study Reference                          | Study Design          | Country/Cohort Details                          | Duration | Participants | Cognitive Assessment | Follow-up | Findings                                                                 |
|----------------------------------------|-----------------------|------------------------------------------------|----------|--------------|----------------------|-----------|--------------------------------------------------------------------------|
| 48. Tyas et al. 2001 [70] Canada       | Longitudinal cohort   | The Manitoba Study of Health and Aging (MSHA); The Canadian Study of Health and Aging (CSHA) | 5 y      | 36 AD        | MMSE                 | 658       | Cognitively healthy 3MSE 74.0 (5.8) Coffee, Tea (NS) retrospective      |
| 49. Valls-Pedret et al. 2012 [23] Spain| Cross-sectional, cohort study | The Prevención con Dieta Mediterránea (PREDIMED) Study | NA       | 447 cognitively healthy | NA; RAVLT – delayed recall | Range: 48% | Coffee retrospective +, better memory function and global cognition with coffee consumption. Coffee: p = 0.016 |
| 50. Van Boxtel et al. 2003 [65] The Netherlands | Longitudinal cohort study | The Maastricht Aging Study (MAAS) | 6 y      | 1,366 cognitively healthy, follow-up | 1,366 cognitively healthy, baseline | VVLT 50.2 (15.4) | Multiple sources (coffee, tea, cola, energy-drink) retrospective |
| 51. Van Gelder et al. 2007 [62] Finland, Italy | Longitudinal cohort study | The Finland, Italy and the Netherlands (FINE) Study cohorts | 10 y     | 531 cognitively healthy | 145 cognitively healthy, non-coffee consumer | MMSE 76.1 (4.2) | Coffee retrospective +, inverse association between low and moderate coffee consumption (<4 cups/day) and cognitive decline. 3 cups/d: p < 0.001 1, 2, 4 cups/d: p < 0.05 5, no effect for high coffee consumption (>4 cups/d), p > 0.05 |
| 52. Vercambre et al. 2013 [72] France | Longitudinal cohort study | The Women’s Antioxidant Cardiovascular Study (WACS) Cohort | 5 y      | X/2,475 cognitively healthy, Q2 caffeine consumer | X/2,475 cognitively healthy, Q1 caffeine consumer | Global cognitive score NA; >65 y | Multiple sources (116 caffeine-containing items, e.g., caffeinated coffee, decaffeinated coffee, tea, chocolate) retrospective |
| 53. Walters & Lesk 2016 [60] UK        | Cross-sectional RCT   | Division of Psychology, University of Bradford database | NA       | 20 cognitively healthy, caffeine consumer | 20 cognitively healthy, placebo | MMSE 73.4 (6.6) | NA Pure caffeine prospective |
| 54. Wang et al. 2017 [54] China        | Longitudinal and cross-sectional cohort study | Elderly in Shanghai (from Huangpu, Changning, Putuo, Pudong districts) | 1 y      | 224 MCI       | 781 cognitively healthy | MMSE 72.7 (8.5) | Tea (NS) retrospective +, tea can protect people >60 y against MCI. OR = 0.59 (0.43–0.82) /

(Continued)
| Study | Study design and length of follow-up | Cohort | Subjects (N and population) | Control (N and population) | Selected cognition measure/ domain | Age (y) | Sex (% men) | Caffeine source consumption | Effect and principle findings (Positive effect+, negative effect -, no effect/) |
|-------|------------------------------------|--------|-----------------------------|----------------------------|----------------------------------|---------|-------------|---------------------------|-------------------------------------------------|
| 55. Wu et al. 2011 [68] Taipei | Cross-sectional cohort study retrospective | The National Health Interview Survey 2005 | X/2,219 subjects, caffeine consumer | X/2,219 subjects, non-caffeine consumer | MMSE | 73.3 (5.9) | 52% | Coffee, Tea (NS) retrospective | +, decreased risk of cognitive impairment with coffee. Coffee: OR = 0.51 (0.31–0.83) |
| 56. Xu et al. 2018 [55] China | Cross-sectional cohort study retrospective | China Longitudinal Aging Study (CLAS) | 439 MCI | 1,692 cognitively healthy | MMSE | 70.9 (7.9) | 45% | Tea (green, black, oolong tea) retrospective | +, protective effect against MCI for green tea consumption in men, particularly at <70 y. Green tea (age <70): OR = 0.376 (0.20–0.70) |
| 57. Yang et al. 2016 [56] China | Cross-sectional cohort study retrospective | Elderly in Zhejiang province | 847 subjects (749 cognitively healthy +98 dementia), tea consumer | 11,68 subjects (822 cognitively healthy+346 dementia), non-tea consumer | MMSE | 79.5 (7.6) | 42% | Tea (NS) retrospective | +, association between tea consumption and AD or severe cognitive impairment. OR = 0.5 (0.4–0.6) |
| 58. Cao et al. 2012 [35] USA | Longitudinal case-control study prospective 2–4 y | Florida Alzheimer’s Disease Research Center (FADRC), Miami and Tampa cohort | 124 subjects (69 cognitively healthy, 32 MCI, 23 dementia), follow-up | 124 subjects (69 cognitively healthy, 32 MCI, 23 dementia), follow-up | MMSE | 74.9 (1.9) | 40% | Multiple sources (Plasma caffeine concentration) retrospective | +, caffeine/coffee intake associated with reduced risk of dementia or delayed onset, particularly for those who already have MCI. p < 0.02 |
| 59. Cho et al. 2018 [22] South Korea | Cross-sectional cohort study retrospective | The Movement Disorders Clinic, Chonnam National University Hospital | 136 PD, coffee consumer | 60 PD, non-coffee consumer | K-MMSE (Korean version) | 66.3 (9.5) | 52% | Coffee retrospective | +, better global cognitive scores for coffee consumption in patients with PD. p = 0.004 |
| 60. Ide et al. 2014 [40] Japan | Longitudinal pilot study prospective 3 months | The White Cross Nursing Home in Higashi-Murayama, Tokyo, Japan 2012 | 12 cognitively impaired (3 AD, 8 VaD, 1 DLB), follow-up | 12 cognitively impaired (3 AD, 8 VaD, 1 DLB), baseline | MMSE-J (Japanese version) | 88 (7.6) | 17% | Green tea powder prospective | +, association between three-month green tea consumption and improved cognitive function or reduced progression of cognitive dysfunction. p = 0.03 |
period of 3 months and 12 months, respectively. Only 'short-term' (3 months) green tea consumption was associated with improved cognitive function or reduced progression of cognitive dysfunction.

Taken together, caffeine has a positive effect on cognition in the majority of studies (34/75%) studies including 272/289 (94%) subjects) including cognitively impaired subjects.

**Caffeine and study characteristics**

**Caffeine source**

Through categorization of caffeine source that were investigated in each study, we found 29 (48%; 103,321 (67%) subjects) coffee-based studies, 30 (49%; 59,309 (39%) subjects) studies based on tea, 15 (25%; 25,928 (17%) subjects) studies based on multiple caffeinated sources, and 2 (3%; 70 (0.05%) subjects) studies based on pure caffeine (Table 2A–D). Further categorization of tea-based studies revealed 13 (21%; 32,295 (21%) subjects) studies assessing green tea, 7 (11%; 19,635 (13%) subjects) studies assessing black tea and/or oolong tea, and 19 (31%; 37,648 (25%) subjects) studies with other or non-specified tea types (Fig. 3). For the coffee-based studies, we found that 8/29 (28%) studies including 29,515/103,321 (29%) subjects reported a positive association of caffeine consumption on the risk of dementia and/or cognitive decline. Furthermore, 11/29 (38%) studies including 31,681/103,321 (31%) subjects indicated that the outcome was dependent on the quantity of coffee consumed (more positive associations with moderate quantities), sex (more positive for women), age (more positive for older age, 65–74 years), and/or the assessment of short- or long-term association (more protective in the short-term than long-term). The remaining studies on coffee (10/29 (34%); 42,125/103,321 (41%) subjects) reported no association between caffeine and risk of dementia and/or cognitive function. Two studies reported negative associations when long-term effects were assessed [64] or when examining change in habitual consumption [77], but these outcomes shifted toward a positive association when assessing short-term effects and a fixed caffeine consumption frequency and/or concentration over time, respectively.

For tea-based studies, we observed 10/30 (33%) studies including 25,381/59,309 (43%) subjects with positive outcomes, 11/30 (37%) studies including 24,556/59,309 (41%) subjects with mixed outcomes dependent on consumed tea source (more positive
for green tea), consumed quantity (more positive with moderate quantities), sex (mixed effects), and/or age (mixed effects). Furthermore, 9/30 (30%) studies including 9,372/59,309 (16%) subjects reported no association between tea intake and cognition. No negative associations were found for tea consumption. By classifying the different tea types, we observed proportionally more beneficial associations for green tea (39%) and other/non-specified tea (37%) compared to black/oolong tea (29%). On the other hand, we found that, across most studies (5/7 (71%) studies including 14,603/19,634 (74%) subjects), black/oolong tea was not associated with dementia/cognitive decline.

Next, we assessed studies that included more than one caffeine source, including coffee, tea, carbonated soft drinks, energy drinks, and foods. Five out of 15 (33%) studies including 6,325/25,928 (24%) subjects reported a protective association and 3/15 (20%) studies including 4,210/25,928 (16%) reported no association between caffeine consumption and cognitive decline. Mixed results were found for 7/15 (47%) studies including 15,393/25,928 (59%) subjects: these studies revealed a dependency of study outcomes according to consumed quantity of caffeine, sex, age, and/or covariates in the models. More positive outcomes were found for women compared to men [71, 74], and more positive associations were found for a moderate or higher caffeine quantity (>62 mg/d [74], >200 mg/d [39], >300 mg/d [71]). We also found that in studies with moderate caffeine sources, more positive effects were found at ages >70 years, and particularly over 90 years. We found inconclusive findings for the impact of univariate-/basic adjustments or multiple adjustments on cognitive function [72, 81, 85].

Finally, two studies assessed the association of pure caffeine consumption: Konishi et al. (2018) reported better executive function scores, while Walters & Lesk (2016) reported no significant association on cognitive tests.

Our examination of effects in coffee, tea, mixed sources, and pure caffeine-based studies demonstrates that the study outcomes are highly dependent on the caffeine source. Among these caffeine sources, only black/oolong tea seems not to have a protective effect for dementia/cognitive decline. In addition, our data reveal that evidence of a deleterious effect of caffeine consumption on cognitive function is limited.

Caffeine consumption quantity

We assessed the associations between caffeine quantity based on the frequency and/or dosage. Of the 61 studies, 48 provided sufficient information to allow assessment of these associations (Table 3, Fig. 3). Based on pre-specified criteria, the studies were divided into three quantity categories: low caffeine consumption (<100 mg/d) (n = 29, N = 68,470), moderate caffeine consumption (100–400 mg/d) (n = 35, N = 111,776), and high caffeine consumption (>400 mg/d) (n = 14, N = 69,039). For studies with low- and high quantities of caffeine consumption, we mainly found no impact on risk of dementia or cognitive function: positive associations were only observed for 11/29 (38%) and 5/14 (36%) studies respectively. Interestingly, for moderate caffeine consumption, we mainly found beneficial associations with cognitive function (27/35 (77%) studies, that were either dependent (16/35 (46%) studies) or independent of type of caffeine source and/or other study characteristics (11/35 (31%) studies). By further stratifying studies using moderate consumption

Fig. 2. Risk of bias assessment of the included studies.

Table 3: Caffeine consumption quantity.
Table 2A  
Association between coffee-based studies \((n = 29)\) and cognitive decline/dementia

| Coffee-based studies | Positive association | No association | Negative association |
|----------------------|----------------------|----------------|----------------------|
| Al-khateeb et al. 2014 [83] | Arab et al. 2011 [32]  
(Sex; men) | Araújo et al. 2015 [79]  
(Caffeine consumption quantity and age; \(\leq 1 \text{ cup/d or } \geq 3 \text{ cups/d, 35–64 years}\)) | Mirza et al. 2014 [64]  
(Caffeine consumption duration; long-term) |
| Arab et al. 2011 [32]  
(Sex; women) | Araújo et al. 2015 [79]  
(Caffeine consumption quantity and age; \(\leq 1 \text{ cup/d or } \geq 3 \text{ cups/d, 35–64 years}\)) | Solfrizzi et al. 2015 [77]  
(Change in habitual intake; increased consumption) |
| Araújo et al. 2015 [79]  
(Caffeine consumption quantity and age; 2 –3 cups/d, 65–74 years) | Araújo et al. 2016 [63]  
(Caffeine consumption duration; long-term) | Broe et al. 1990 [78]  
(Caffeine consumption duration; short-term) |
| Araújo et al. 2016 [63]  
(Caffeine consumption duration; short-term) | Chuang et al. 2019 [66]  
(Caffeine consumption quantity and sex; \(\geq 7 \text{ times/ wk, women}\)) | Dong et al. 2020 [50]  
(Caffeine consumption quantity; \(< 266.4 \text{ g/d}\)) |
| Cho et al. 2018 [22] | Dong et al. 2020 [50]  
(Caffeine consumption quantity; \(< 266.4 \text{ g/d}\)) | Eskelinen et al. 2009 [28]  
(Caffeine consumption quantity; \(<3 \text{ cups/d and } \geq 5 \text{ cups/d}\)) |
| Chuang et al. 2019 [66]  
(Caffeine consumption quantity and sex; \(\geq 7 \text{ times/wk, women}\)) | Fischler et al. 2018 [80]  
(Caffeine consumption quantity; \(\geq 7 \text{ times/wk, women}\)) | Haller et al. 2018 [87]  
(Caffeine consumption quantity; \(<28 \text{ cups/months}\)) |
| Dong et al. 2020 [50]  
(Caffeine consumption quantity; 266.4–495 g/d or \(\geq 495 \text{ g/d}\)) | Eskelinen et al. 2009 [28]  
(Caffeine consumption quantity; \(<3 \text{ cups/d and } \geq 5 \text{ cups/d}\)) | Geler et al. 2011 [24]  
(Caffeine consumption quantity; \(<3 \text{ cups/d and } \geq 5 \text{ cups/d}\)) |
| Eskelinen et al. 2009 [28]  
(Caffeine consumption quantity; 3–5 cups/d) | Haller et al. 2018 [87]  
(Caffeine consumption quantity; \(<28 \text{ cups/months}\)) | Jarvis 1993 [57]  
(Caffeine consumption quantity; \(<3 \text{ cups/d and } \geq 5 \text{ cups/d}\)) |
| Haller et al. 2018 [87]  
(Caffeine consumption quantity; \(<28 \text{ cups/months}\)) | Haller et al. 2018 [87]  
(Caffeine consumption quantity; \(<28 \text{ cups/months}\)) | Mirza et al. 2014 [64]  
(Caffeine consumption quantity; \(1–3 \text{ cups/d}\)) |
| Johnson-Kozlow et al. 2002 [38]  
(Sex; women) | Johnson-Kozlow et al. 2002 [38]  
(Sex; men) | Kuriyama et al. 2006 [43]  
(Caffeine consumption quantity; \(<3 \text{ cups/d and } \geq 5 \text{ cups/d}\)) |
| Lee et al. 2017 [67]  
(Lindsay, 2002 [69]) | Larisatu et al. 2009 [61]  
(Caffeine consumption quantity; \(<3 \text{ cups/d and } \geq 5 \text{ cups/d}\)) | Larsson & Wolk 2018 [86]  
(Caffeine consumption quantity; \(<3 \text{ cups/d and } \geq 5 \text{ cups/d}\)) |
| Mirza et al. 2014 [64]  
(Caffeine consumption quantity and caffeine consumption duration; \(>3 \text{ cups/d, short-term}\)) | Solfrizzi et al. 2015 [77]  
(Caffeine consumption quantity; \(1–2 \text{ cups/d}\)) | Ng et al. 2008 [76]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) |
| Solfrizzi et al. 2015 [77]  
(Caffeine consumption quantity; \(1–2 \text{ cups/d}\)) | Solfrizzi et al. 2015 [77]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) | Noguchi-Shinohara et al. 2014 [44]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) |
| Sugiyama et al. 2016 [46] | Shirai et al. 2020 [45]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) | Noguchi-Shinohara et al. 2014 [44]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) |
| Valls-Pedret et al. 2012 [23] | Shirai et al. 2020 [45]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) | Shirai et al. 2020 [45]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) |
| Van Gelder et al. 2007 [62]  
(Caffeine consumption quantity; <4 cups/d) | Solfrizzi et al. 2015 [77]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) | Shirai et al. 2020 [45]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) |
| Wu et al. 2011 [68] | Solfrizzi et al. 2015 [77]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) | Shirai et al. 2020 [45]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) |
| Tyas et al. 2001 [70] | Solfrizzi et al. 2015 [77]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) | Shirai et al. 2020 [45]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) |
| Van Gelder et al. 2007 [62]  
(Caffeine consumption quantity; >4 cups/d) | Van Gelder et al. 2007 [62]  
(Caffeine consumption quantity; >4 cups/d) | Shirai et al. 2020 [45]  
(Caffeine consumption quantity; \(<1 \text{ cup/d}\)) |

Bold studies indicate multiple outcomes.

according to caffeine sources (Table 3), we found that especially consumption of green tea may reduce the risk of dementia and cognitive decline.

**Confounding factors**

Most studies adjusted for age and sex, and in a subset of studies additional model adjustments were made for factors like hypertension, diabetes mellitus, hyperlipidemia, education, APOE genotype, smoking, alcohol, physical activities, body mass index (BMI), socioeconomic status, and global cognition (MMSE). Some studies reported an impact of confounding factors on outcomes.

For seven studies [32, 38, 52, 55, 66, 71, 74], outcomes were dependent on sex. These studies reported that beneficial associations are predominantly found...
Table 2B
Association between tea-based studies \((n = 30)\), subdivided into green tea \((n = 13)\), black/oolong tea \((n = 7)\), and other or non-specified tea types \((n = 19)\) and cognitive decline/dementia

| Positive association | No association | Negative association |
|----------------------|----------------|----------------------|
| **Green tea**        |                |                      |
| Ide et al. 2014 [40] |                |                      |
| Gu et al. 2018 [51]  | Ide et al. 2016 [41]  |
| (Caffeine consumption quantity and type of tea source; \(>5\) times/wk) | Fischer et al. 2018 [80]  |
| Kuriyama et al. 2006 [43]  | Gu et al. 2018 [51]  |
| (Caffeine consumption quantity and type of tea source; \(\geq 2\) cups/d) | Kuriyama et al. 2006 [43]  |
| Lee et al. 2017 [67] | Shen et al. 2015 [53]  |
| Ng et al. 2008 [76]  | Shirai et al. 2020 [45]  |
| **Noguchi-Shinohara et al. 2014** [44]  | Tomata et al. 2016 [47]  |
| (Type of tea source) | Xu et al. 2018 [55]  |
| **Shirai et al. 2020** [45]  | (Sex and age; women, \(\geq 70\) years) |
| (Caffeine consumption quantity; 2–3 times/d and \(\geq 4\) times/d) | (Caffeine consumption quantity; \(<2\) cups/d) |
| Tomata et al. 2016 [47]  |                |                      |
| (Caffeine consumption quantity and type of tea source; \(>2\) cups/d) |                  |
| Xu et al. 2018 [55]  |                |                      |
| (Type of tea source, sex and age; men, \(<70\) years) |                  |

| **Black/Oolong tea** |                |                      |
| Ng et al. 2008 [76]  | Feng et al. 2018 [25]  |
| Shen et al. 2015 [53]  | Kuriyama et al. 2006 [43]  |
| (Type of tea source) | (Type of tea source) |
| **Noguchi-Shinohara et al. 2014** [44]  | Tomata et al. 2016 [47]  |
| (Type of tea source) | Xu et al. 2018 [55]  |
| **Shirai et al. 2020** [45]  |                |                      |
| (Caffeine consumption quantity and type of tea source; \(>2\) cups/d) |                  |
| **Xu et al. 2018** [55]  |                |                      |
| (Type of tea source) |                  |

| **Other/non-specified tea type** |                |                      |
| Arab et al. 2011 [32]  | Arab et al. 2011 [32]  |
| (Sex; women) | (Sex; men) |
| Chen et al. 2012 [49]  | Broe et al. 1990 [78]  |
| Chin et al. 2008 [82]  | Chuang et al. 2019 [66]  |
| (Caffeine consumption quantity and sex; \(\geq 7\) times/wk, women) | (Caffeine consumption quantity and sex; \(2–6\) times/wk, men) |
| Feng et al. 2012 [75]  | Dai et al. 2006 [36]  |
| Huang et al. 2009 [52]  | Eskelinen et al. 2009 [28]  |
| (Sex; men) | Gu et al. 2018 [51]  |
| Jarvis 1993 [57]  | Huang et al. 2009 [52]  |
| (Sex; women) | (Type of tea source) |
| Lee et al. 2017 [67]  | Lindsay 2002 [69]  |
| Nurk et al. 2009 [84]  | Shen et al. 2015 [53]  |
| (Caffeine consumption quantity; \(<2\) cups/d) |                  |

(Continued)
Table 2B (Continued)

| Positive association | No association | Negative association |
|----------------------|---------------|----------------------|
| Shen et al. 2015 [53] | Tyas et al. 2001 [70] |
| (Caffeine consumption quantity; 2–4 cups/d and ≥4 cups/d) |
| Wang et al. 2017 [54] | Wang et al. 2017 [54] |
| (Age; ≥60 years) |
| Yang et al. 2016 [56] | Wu et al. 2011 [68] |

Bold studies indicate multiple outcomes.

Table 2C
Association between multiple caffeinated sources (n = 15) and cognitive decline/dementia

| Positive association | No association | Negative association |
|----------------------|---------------|----------------------|
| Beydoun et al. 2014 [33] | Beydoun et al. 2014 [33] |
| (Age; ≥70 years) | (Age; <70 years) |
| Boot et al. 2013 [34] |
| Corley et al. 2010 [85] | Corley et al. 2010 [85] |
| (Model; adjustment for age and sex only) | (Model; multiple additional adjustments) |
| Driscoll et al. 2016 [37] |
| Iranpour et al. 2020 [81] | Iranpour et al. 2020 [81] |
| (Model; no adjustments) |
| Paganini-Hill et al. 2016 [39] | Paganini-Hill et al. 2016 [39] |
| (Caffeine consumption quantity and age; 60–199 mg/d, 70 years) |
| Maia & de Mendonça 2002 [73] | Ritchie et al. 2007 [71] |
| (Caffeine consumption quantity and sex; <300 mg/d, men) |
| Paganini-Hill et al. 2016 [39] | Santos et al. 2010 [74] |
| (Caffeine consumption quantity and age; ≥200 mg/d, 90 years) | (Caffeine consumption quantity and sex; <62 mg/d, men) |
| Ritchie et al. 2007 [71] |
| (Caffeine consumption quantity and sex; >300 mg/d, women) |
| Santos et al. 2010 [74] | Verambre et al. 2013 [72] |
| (Caffeine consumption quantity and sex; >62 mg/d, women) | (Model; adjustment for age, education and energy from diet only) |
| Smith 2009 [39] |
| Verambre et al. 2013 [72] |
| (Model; multiple additional adjustments) |

Bold studies indicate multiple outcomes.

Table 2D
Association between pure caffeine (n = 2) and cognitive decline/dementia

| Pure caffeine | |
|---------------|---|
| Positive association | No association | Negative association |
| Konishi et al. 2018 [48] | Walters & Lesk 2016 [60] |

in women (5/7 studies). In line with these findings, two studies with only female participants [37, 72] reported positive associations and two out of three studies with only male participants [24, 25, 62] reported no associations.

Four studies indicated that positive associations are dependent on age. These studies reported positive associations between caffeine consumption and dementia and/or cognitive function at older ages (65–74 years versus 35–64 years [79], ≥70 years versus <70 years [33], 90 years versus 70 years [39]). However, two other studies indicated the reverse, an effect at younger age (>60 years versus >70 years [54]) or that effects were particularly found at ages <70 years old [55].

Furthermore, Mirza et al. (2014) [64] and Araújo et al. (2016) [63] found different outcomes depending on the time of follow-up. Short-term follow-up (within 4 years) revealed positive associations, while the association was negative at long-term follow-up...
## Table 3

**Association between caffeine consumption quantity and cognitive decline/dementia**

### Low caffeine consumption

(<100 mg/d)

| Studies                  | Caffeine source | Quantity | Association (+, /, –) |
|--------------------------|-----------------|----------|-----------------------|
| Arab et al. 2011 [32]    | Tea (NS), Coffee | 0.57 cups/d | + (women), 0.95 cups/d (men) |
| Araújo et al. 2015 [79]  | Coffee          | ≤1 cup/d  | /                     |
| Araújo et al. 2016 [63]  | Coffee          | 0–1 cup/d | /                     |
| Chuang et al. 2019 [66]  | Tea (NS), Coffee | 2–6 cups/wk | /                     |
| Dai et al. 2006 [36]     | Tea (NS)        | ≥3 cups/wk | /                     |
| Dong et al. 2020* [50]   | Coffee          | 1–266.4 mg/d | /                     |
| Feng et al. 2018 [25]    | Tea (Black)     | 1 cup/wk  | /                     |
| Gu et al. 2018 [51]      | Tea (Green), Tea (NS) | 1–5 times/wk | /                     |
| Haller et al. 2018 [87]  | Coffee          | <28 cups/month | /                     |
| Ide et al. 2014 [40]     | Tea (Green tea powder) | 2 g/d (<100 mg/d caffeine) | + |
| Ide et al. 2016 [41]     | Tea (Green tea powder) | 2 g/d (<100 mg/d caffeine) | / |
| Iranpour et al. 2020 [81]| Multiple sources | 11–102 mg/d | /                     |
| Kitamura et al. 2016 [42]| Tea (Green)     | 1–6 cups/wk | +(univariate model), / (multiple additional adjustments) |
| Kuriyama et al. 2006 [43]| Tea (Green), Tea (Black/oolong) | <1 cup/d | /                     |
| Lee et al. 2017* [67]    | Tea (Green), Tea (Black/oolong) | >3 cups/wk | + |
| Lesk et al. 2009 [58]    | Multiple sources | Mean: 70.3 (±36.2) mg/d | / |
| Maia & de Mendonça, 2002 [73]| Multiple sources | Mean: 73.9 (±97.9) mg/d | + |
| Ng et al. 2008 [76]      | Tea (Green), Tea (Black/oolong) | <1 cup/d | + |
| Noguchi-Shinohara et al. 2014 [44]| Tea (Green) | <1 cup/d | + |
| Paganini-Hill et al. 2016* [39]| Multiple sources | 50–199 mg/d | / |
| Ritchie et al. 2007* [71]| Multiple sources | 100–200 mg/d | / |
| Santos et al. 2010 [74]  | Multiple sources | 22–62 mg/day | / |
| Shen et al. 2015 [53]    | Tea (Black), Tea (Green) | <2 cups/d | / |
| Shirai et al. 2020 [45]  | Tea (Green)     | 2–3 times/d | + |
| Solfrizzi et al. 2015* [77]| Coffee         | 1 cup/d   | /                     |
| Tomata et al. 2016 [47]  | Tea (Green), Tea (Black/oolong) | 1–2 cups/d | / |
| Valls-Pedret et al. 2012 [23]| Coffee         | Median: 21 ml/d | + |
| Wu et al. 2011 [68]      | Coffee          | >1 cup/wk  | +                     |
| Tea (NS)                 |                 |           | /                     |
| Xu et al. 2018 [55]      | Tea (Green)     | >3 cups/wk | +(men, particularly <70 years), / (women) |
|                          | Tea (Black/oolong) |           | /                     |

### Moderate caffeine consumption

(100–400 mg/d)

1–4 cups coffee/d or 3–10 cups tea/d

| Studies                  | Caffeine source | Quantity | Association (+, /, –) |
|--------------------------|-----------------|----------|-----------------------|
| Araújo et al. 2015 [79]  | Coffee          | 2–3 cups/d | +(65–74 years), / (35–64 years) |
| Araújo et al. 2016 [63]  | Coffee          | 1–3 cups/d | /                     |
| Beydoun et al. 2014 [33] | Multiple sources | Mean: 132 mg/d | +(≥70 years), / (<70 years) |
| Bree et al. 1990 [78]    | Tea (NS)        | >4 cups/d | /                     |
| Chin et al. 2008 [82]    | Tea (NS)        | Mean: 4.46 cups/d | + |
| Chuang et al. 2019* [66] | Tea (NS), Coffee | ≥7 cups/wk | +(all subjects and women), / (men) |
| Corley et al. 2010 [85]  | Multiple sources | Mean: 182.5 mg/d | +(adjustment for age and ), sex/multiple additional ) adjustments |
| Dong et al. 2020* [50]   | Coffee          | 266.4–295 mg/d | + |
| Driscoll et al. 2016 [37]| Multiple sources | Mean: 261 mg/d | + |

(Continued)
Table 3 (Continued)

| Studies                        | Caffeine source | Quantity | Association (+, /, –) |
|-------------------------------|-----------------|----------|-----------------------|
| Eskelinen et al. 2009a [28]   | Coffee          | 3–5 cups/d | +                     |
| Feng et al. 2018a [25]        | Tea (Black)     | >1 cup/d  | /                     |
| Gelber et al. 2011 [24]       | Coffee, Multiple sources | 115.5–188.0 mg/d | / |
| Gu et al. 2018 [51]           | Tea (Green)     | >5 times/wk | +                     |
|                               | Tea (NS)        |          | /                     |
| Haller et al. 2018 [87]       | Coffee          | 29–60 cups/mo | +                     |
| Iranpour et al. 2020 [81]     | Multiple sources | >200 mg/d | (+univariate model), / (multiple additional adjustments) |
| Johnson-Kozlow et al. 2002 [38] | Coffee | Mean: 3 cups/d | + (women), / (men) |
| Kitamura et al. 2016a [42]    | Tea (Green)     | >1 cup/d  | +                     |
| Konishi et al. 2018 [48]      | Pure caffeine  | 200 mg/d  | +                     |
| Kuriyama et al. 2006 [43]     | Tea (Green)     | ≥ 2 cups/d | +                     |
|                               | Tea (Black/oolong), Coffee |          | /                     |
| Larsson & Wolk, 2018a [86]    | Coffee          | 1.0–4.9 cups/d | /                     |
| Lindsay, 2002 [69]            | Coffee          | >1 cup/d  | +                     |
|                               | Tea (NS)        |          | /                     |
| Mirza et al. 2014 [64]        | Coffee          | 1–3 cup/d | /                     |
| Ng et al. 2008 [76]           | Tea (Green),    | >1 cup/d  | +                     |
|                               | Tea (Black/oolong) |          | /                     |
|                               | Coffee          |          | /                     |
| Noguchi-Shinohara et al. 2014 [44] | Tea (Green) | >1 cup/d | +                     |
| Paganini-Hill et al. 2016 [39] | Multiple sources | >200 mg/d | (+>90 years), / (>70 years) |
| Ritchie et al. 2007 [71]      | Multiple sources | 200–300 mg/d | /                     |
| Santos et al. 2010a [74]      | Multiple sources | >62 mg/day | (+women), / (men) |
| Shen et al. 2015 [53]         | Tea (Black)     | ≥ 4 cups/d | +                     |
|                               | Tea (Green)     | ≥ 4 times/d | +                     |
|                               | Coffee          | ≥ 2 times/d | /                     |
| Smith, 2009 [59]              | Multiple sources | Mean: 140 mg/d | +                     |
| Solfirzzi et al. 2015 [77]    | Coffee          | 1–2 cups/d | +                     |
| Sugiyama et al. 2016 [46]     | Coffee          | 1–2 cups/d | +                     |
| Tomata et al. 2016 [47]       | Tea (Green)     | ≥ 5 cups/d | +                     |
|                               | Tea (Black/oolong) |          | /                     |
| Van Gelder et al. 2007 [62]   | Coffee          | 1–4 cups/d | +                     |
| Walters & Lesk, 2016 [60]     | Pure caffeine  | 200 mg/d  | /                     |

**High caffeine consumption**

(>400 mg/d)

| Studies                        | Quantity | Association (+, /, –) |
|-------------------------------|----------|-----------------------|
| Araújo et al. 2015a [79]      | ≥ 3 cups/d | /                     |
| Araújo et al. 2016a [63]      | ≥ 3 cups/d | +(short-term), / (long-term) |
| Broe et al. 1990 [78]         | ≥ 4 cups/d | /                     |
| Dong et al. 2020 [50]         | ≥ 495 mg/d | +                     |
| Eskelinen et al. 2009 [28]    | ≥ 5 cups/d | /                     |
| Gelber et al. 2011 [24]       | 415–2673 mg/d | /                     |
|                               | Multiple sources |          | /                     |
| Haller et al. 2018a [87]      | 61–168 cups/mo | /                     |
| Laitala et al. 2009 [61]      | Mean: 5.3 cups/d | /                     |
| Larsson & Wolk, 2018a [86]    | ≥ 5.0 cups/d | /                     |
| Mirza et al. 2014a [64]       | >3 cups/d  | +(short-term), / (long-term) |
| Ritchie et al. 2007a [71]     | >300 mg/d  | +(women), / (men) |
| Van Boxtel et al. 2003 [65]   | Median: 5–6 cups/d | /                     |
| Van Gelder et al. 2007 [62]   | >4 cups/d  | /                     |
| Vercambre et al. 2013 [72]    | >371 mg/d  | +                     |

*aCategorization in this group due to different categories used in the study.*
Corley et al. (2010) [85] observed protective associations between caffeine and cognitive function when adjusting for age and sex, but when additional adjustments were made for socioeconomic status or social class and (childhood) IQ, the association did not reach the threshold for statistical significance. Similar results were observed by Iranpour et al. (2020) [81], who reported a positive association in a univariate model but no association in models where adjustments for factors like sex, age, race/ethnicity, education, and marital status, or self-rated health, disease history, and depression were made. Vercambre et al. (2013) [72], on the other hand, only found a positive association when adjusting for alcohol consumption, physical activity, BMI, and smoking, but not when only adjusting for age, education, and diet. Moreover, this study found a more pronounced positive association with caffeine when it was supplemented with vitamin B.

DISCUSSION

In this systematic review, we assessed the association between caffeine and 1) the risk of dementia and/or cognitive decline and 2) cognitive function in individuals with impaired cognition (i.e., MCI or dementia). The number of studies showing positive associations (dependent or independent of study characteristics) was 46/57 (81%) including 111,926/153,070 (73%) subjects, indicating that caffeine has a beneficial effect on the risk of dementia/cognitive decline. We also found more positive results (3/4 (75%) studies including 272/289 (94%) subjects) for studies that included subjects with MCI, or any type of dementia, indicating that caffeine also has a beneficial effect in cognitively impaired subjects.
Furthermore, we observed that various study characteristics affect the reported associations of caffeine such that moderate consumption seems to be more beneficial than low- or high quantities, and coffee, green- and other/non-specified tea, and multiple caffeinated sources are more beneficial than other caffeine sources like black/oolong tea. Effects were also found to be more pronounced in women compared to men, and many studies reported mixed outcomes based on other factors like age and follow-up time. Across all studies, we observed only two studies with a negative effect, suggesting that caffeine is unlikely to negatively affect cognition or dementia risk. This review highlights that dietary factors may influence risk of cognitive decline and dementia, and may also aid the future development of caffeine-based intervention studies, which might serve as a cost-effective alternative or add-on to other non-pharmaceutical or pharmacological treatments against cognitive decline and dementia (e.g., physical activity [88]).

Potential mechanisms

Results from this review suggest that caffeine effects are dependent on the caffeine source and quantity. Several explanations exist for this outcome. First, different types of caffeine sources contain different levels of caffeine [29], and low dosages might be inadequate to convey positive effects while with excessive dosages the negative effects (e.g., anxiety) might outweigh the positive effects. There might also be individual variability in the physiological response to caffeine (e.g., due to genetic factors that influence responsiveness of A_{2A} receptors), which would result in differential effects of the same dose of caffeine across individuals [14, 89, 90]. Further-
more, physiological effects of other substances than caffeine that are contained within the caffeine source (e.g., coffee) may influence or strengthen the caffeine response, by affecting the kinetics of caffeine in the body and the response of adenosine receptors, or have a caffeine independent effect that influences cognitive performance [91]. For example, various sources of caffeine contain antioxidants, which have been found to play a role in protecting against oxidative stress, and may thereby help in preventing cognitive deterioration [92]. Coffee displays antioxidative effects through chlorogenic acid and polyphenols [93]. Tea displays antioxidative effects through tea catechins and theaflavins, and green tea exhibits higher antioxidative effects than black or oolong tea [94]. Varying antioxidative mechanisms or degrees of antioxidative effects might contribute to the differences in study effects according to caffeine sources observed in this report (i.e., more effects in green compared to black/oolong tea). However, further research is needed on the effect of antioxidants as studies have also reported no effect of antioxidants on cognitive function, but rather on mood [95]. Caffeine may also lead to better cognitive function and memory indirectly through an increase in alertness and wakefulness [12], and by influencing sleep and impulsivity [14, 96].

Caffeine has also been found to influence neural and vascular activity such as vasoconstriction and reduction in cerebral blood flow (CBF). Reduction in CBF leads to an increased oxygen extraction from the blood to cerebral structures in the brain [97], which, in turn, enhances cognitive performance. It seems possible that a sufficient quantity must be ingested in order to produce this effect. On the other hand, excessive caffeine consumption could lead to (acute) caffeine overdose, which could convey negative effects such as reactive oxygen species formation [98], that outweigh the positive, or indirect negative symptoms that could influence cognitive function such as restlessness, anxiety, agitation, insomnia, and headache [16].

This review revealed incongruent outcomes for other confounding factors such as sex, age, and follow-up time. It seems that caffeine consumption is particularly beneficial for cognitive function in women in comparison with men. In general, inconsistent results for women and men might be explained through sex-based biological variations such as testosterone and estrogen hormone levels [99]. Furthermore, four studies reported an outcome that was dependent on age, but it remains to be determined at what age caffeine has the most beneficial effect as some studies reported greater effects in older subjects, while others reported greater effects in younger subjects. Follow-up time was also found to influence outcomes in two studies. These studies both reported beneficial associations at a short follow-up time, while no effects were observed at a long-term follow up. This suggests that the beneficial effects of caffeine might be temporary.

Strengths and limitations

The main strength is that we performed a systematic review and assessed all available studies, regardless of study design. Thereby, we were able to include more studies than have previously been included in other reviews and meta-analyses [100–103]. However, there are also limitations that need to be considered when interpreting this review. First of all, it is important to highlight that, in the secondary analysis on cognitively impaired individuals, we were able to assess only four studies, and that these studies included individuals with different types of cognitive impairments, various caffeine sources and different study designs. Also, one out of four studies included patients with PD, for which the degrading underlying mechanisms are different compared to patients with dementia or MCI. Secondly, our approach of providing this systematic review did not allow us to perform formal statistical analyses to assess the effects of caffeine quantitatively, or statistically assess modifying effects. This lack of quantitative assessments means our findings were based exclusively on overall study outcomes. Thirdly, our interpretation of the included studies relied on data provided in the paper, and we did not contact the authors to provide additional information because of the wide inclusion timeframe of this review (1990–2020). As a result, not all studies could be included when assessing study characteristics. For example, accurate information on caffeine quantity was not always provided. Furthermore, many studies employed self-reported caffeine consumption data resulting in a high risk of bias due to deviations from the intended intervention. Finally, information on reporting of funding sources and conflicts of interests were not considered as possible confounders in the analyses.

Conclusion

Our findings indicate that caffeine beneficially affects cognitive function and risk of dementia and
that this effect is dependent on the type of caffeine source (e.g., more effects for coffee and green tea), quantity (more effects with moderate quantities), and sex (more effects in female subjects). Furthermore, we found that other factors such as age and follow-up time might influence effects and it is important for future studies to examine, and account for, these confounders. Ideally, future investigation should implement a randomized-controlled trial design, which would allow for quantitative assessments of effects across studies. Future studies including various dosage levels could additionally help to extend our findings regarding the most beneficial caffeine dosage by accurately determining the optimal caffeine quantity to effect cognitive decline and risk of dementia. Furthermore, it would be interesting to map genetic factors that influence response to caffeine (e.g., A2A receptor haplotype) in future studies, as differences in responsiveness to caffeine could influence effects of caffeine on cognition. These insights may help in tailoring cost-effective lifestyle interventions, and possibly even aid in the development of pharmacological interventions that combat cognitive decline and dementia.

DISCLOSURE STATEMENT

Authors’ disclosures available online (https://www.j-alz.com/manuscript-disclosures/20-1069).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-201069.

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