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Caffeine Intake from Coffee or Tea and Cognitive Disorders: A Meta-Analysis of Observational Studies

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Key Words
Caffeine · Coffee · Tea · Cognitive disorders · Dementia · Alzheimer's disease · Cognitive impairment · Cognitive decline · Meta-analysis

Abstract
Background: Observational epidemiological studies such as cross-sectional, case-control, and cohort studies have reported inconsistent findings regarding the association between caffeine intake from coffee or tea and the risk of cognitive disorders such as dementia, Alzheimer's disease, cognitive impairment, and cognitive decline. ***Methods:*** We searched PubMed and EMBASE in September 2014. Three evaluators independently extracted and reviewed articles, based on predetermined selection criteria. ***Results:*** Out of 293 articles identified through the search and bibliographies of relevant articles, 20 epidemiological studies from 19 articles, which involved 31,479 participants (8,398 in six cross-sectional studies, 4,601 in five case-control studies, and 19,918 in nine cohort studies), were included in the final analysis. The pooled odds ratio (OR) or relative risk (RR) of caffeine intake from coffee or tea for cognitive disorders (dementia, Alzheimer's disease, cognitive impairment, and cognitive decline) was 0.82 (95% confidence interval [CI], 0.67–1.01, I^2 = 63.2%) in a random-effects meta-analysis. In the subgroup meta-analysis by caffeine sources, the summary OR or RR of coffee intake was 0.83 (95% CI, 0.70–0.98; I^2 = 44.8%). However, in the subgroup meta-analysis by study design, the summary estimates (RR or OR) of coffee intake for cognitive disorders were 0.70 (95% CI, 0.50–0.98; I^2 = 42.0%) for cross-sectional studies, 0.82 (95% CI, 0.55–1.24; I^2 = 33.4%) for case-control studies, and 0.90 (95% CI, 0.59–1.36; I^2 = 60.0%) for cohort studies. ***Conclusions:*** This meta-analysis found that caffeine intake from coffee or tea was not associated with the risk of cognitive disorders.

Introduction

Dementia is a clinical syndrome characterized by multiple cognitive deficits such as deterioration in memory, language, thinking, and behavior severe enough to interfere with daily activities. According to a recent survey, dementia is the second leading health concern among adults following cancer [1]. Dementia is an age-

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related neurodegenerative disease, mainly developing in people over 65 years. The two most common forms of dementia are Alzheimer's disease (AD) and vascular dementia. Cognitive disorders such as dementia, cognitive impairment, and cognitive decline are known to be caused by complex interactions of genetic factors and environmental factors such as dietary habits, psychosocial activities, educational levels, and various medical diseases [2]. Because the pharmacologic treatments are limited, clinicians have paid attention to modifiable risk factors such as hypertension, dyslipidemia, diabetes mellitus, obesity, and lifestyle to prevent or delay the onset of cognitive disorders [2, 3]. Regarding lifestyle factors, it has been reported that smoking [4], moderate wine consumption [2], lack of exercise [2, 5], and some nutrients (food or supplements) [3, 6] are associated with the risk of cognitive disorders. Recently, the potential effect of caffeine on brain function has become an important issue.

Caffeine is found in numerous foods and beverage items such as coffee, tea, soft drinks, chocolates, and candy bars. Among those, coffee and tea are the leading dietary sources of caffeine. [7]. Caffeine mainly acts upon the central nervous system, increasing arousal and concentration and decreasing fatigue [7]. Although its long-term effects are not yet fully understood, a number of animal studies have suggested that caffeine has neuroprotective effects [8–10]. Regarding the biological effect of caffeine, it acts as a nonselective A_1 and A_{2A} adenosine receptor antagonist and stimulates cholinergic neurons. A blockade of A_{2A} receptors is likely to have a neuroprotective effect from amyloid-β-induced cognitive deficits [10]. As proof of this hypothesis, caffeine intake lowered brain amyloid-β levels in AD-transgenic mice [8]. As for the association between caffeine and cognitive disorders in general populations, epidemiological studies [11–25] such as cross-sectional studies, case-control studies, and cohort studies have reported inconsistent findings. Some studies have suggested that caffeine intake from coffee or tea is inversely associated with the risk of AD, cognitive impairment, or cognitive decline. However, other studies have reported no association.

Several systematic reviews [26–28] and meta-analyses [26, 29, 30] on this issue have been reported. In 2010, a meta-analysis of 11 observational studies [30] suggested that caffeine intake is marginally associated with a decreased risk of cognitive impairment or decline with a summary relative risk (RR) of 0.84 (95% confidence interval [CI], 0.72–0.99, $I^2 = 42.6\%$). However, it included only coffee as caffeine sources and used only the most precise (i.e., the narrowest 95% CIs) ORs or RRs among the results of the included studies, regardless of the exposure sources, levels of exposure, and outcomes assessed, which might cause biases.

In this study, we aimed to investigate the association between caffeine intake from coffee or tea and the risk of cognitive disorders such as dementia, AD, cognitive impairment, and cognitive decline by using meta-analysis of the recently published epidemiological studies with subgroup meta-analysis by various factors.

Methods

Literature Search

We searched PubMed and EMBASE from inception to September 2014 using keywords related to caffeine and cognitive disorders. The keywords were as follows: 'coffee,' 'caffeine,' or 'tea' and 'dementia,' 'Alzheimer Disease,' 'mild cognitive impairment (MCI),' or 'cognitive decline'. We also reviewed the bibliographies of relevant articles for additional publications. The language of publications was restricted to English.

Selection Criteria

We selected observational epidemiologic studies reporting the relationships between caffeine consumption from coffee or tea intake (not caffeine-containing pill supplements) and cognitive disorders such as AD, cognitive impairment, and cognitive decline in human adults by using adjusted relative risks (RRs) or odds ratios (ORs) with confidence intervals (CIs). We included cross-sectional, case-control, and cohort studies.

For the articles selected from the first selection process based on the predetermined criteria, we reviewed the full text and then excluded studies with insufficient data or irrelevant ones. If data were duplicated or shared in more than one study, the first published or more comprehensive study was included in the analysis. Three of us (Y.-S.K., S.M.K., and S.-K.M.) independently evaluated the eligibility of all studies retrieved from the databases according to the selection criteria. Disagreements between evaluators were resolved by discussion.

Data Synthesis and Meta-Analysis

We investigated the association between caffeine intake (highest vs. lowest intake) and the risk of cognitive disorders as a main analysis. In the current study, main outcome measures were classified into four categories (dementia, AD, cognitive impairment, and cognitive decline). If a study reported both coffee and tea intake rather than caffeine intake, coffee was chosen as a surrogate marker because the amount of caffeine in coffee is probably at least two times higher than in tea [12, 21, 24].

In addition, we performed subgroup meta-analyses based on the following factors: study design (cross-sectional vs. case-control vs. cohort), caffeine source (coffee vs. tea), type of outcome (dementia vs. AD vs. cognitive impairment vs. cognitive decline), race of participants (Asian vs. Caucasian), gender (male vs. female), methodological quality of the study (high vs. low), dosage of caffeine intake (lowest vs. moderate vs. highest), and frequency of caffeine intake (daily vs. not daily) by type of caffeine source.

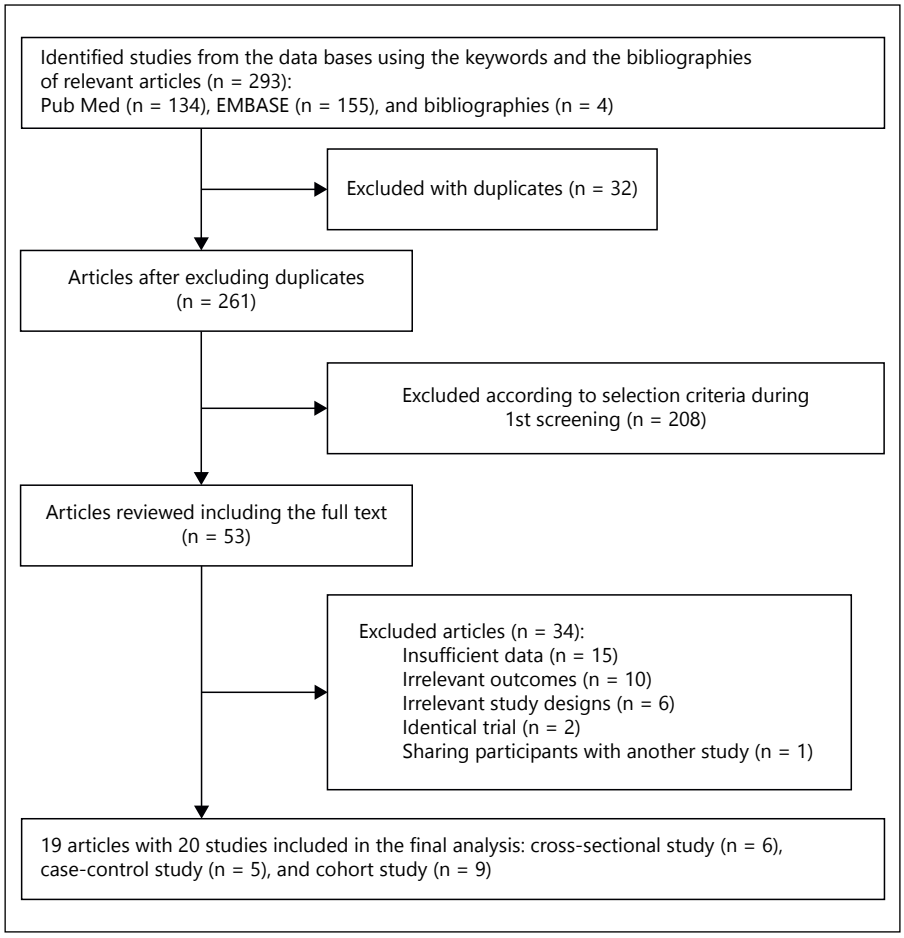

Fig. 1. Flow diagram of identification of relevant studies.

Assessment of Methodological Quality

We assessed the methodological quality of 14 studies (five case-control and nine cohort studies) based on the Newcastle-Ottawa Scale (NOS) for nonrandomized studies in meta-analysis [31]. The NOS comprises 8 items with 3 subscales: the selection of the study groups (4 items), the comparability of the groups (1 item), and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively (3 items). It has a 'star' system, which ranges 0 to 9 stars for the assessment: each study is awarded a maximum of 1 star for each numbered item within the selection and exposure categories, while a maximum of 2 stars can be given for the comparability category. Also, subgroup analyses by study quality were performed.

Statistical Analysis

To compute a pooled OR/RR with a 95% CI, we used an adjusted OR/RR with a 95% CI presented in each article. We evaluated heterogeneity in results across studies using Higgins I^2 [32]. I^2 ranges between 0% (no heterogeneity) and 100% (maximal heterogeneity). An I^2 value >50% was considered having substantial heterogeneity.

The pooled OR/RR with 95% CI was calculated on the basis of both the fixed- and random-effects models. When there was no substantial heterogeneity, we reported the pooled estimates calculated based on the fixed-effects model using the Woolf's method (inverse variance); when there was substantial heterogeneity, we reported the pooled estimates calculated based on the random-effects model using the DerSimonian and Laird method.

Publication bias was evaluated by using a Begg's funnel plot and an Egger's test [33, 34]. Funnel plots are scatter plots of the log odds ratios or log relative risks (i.e., effect sizes) on the X-axis against the sample sizes (or standard errors or 1/standard error; a measure of precision) of each studies on the Y-axis. If publication bias is absent, the log odds ratios or log relative risks of small studies scatter widely at the bottom of the graph, with the spread narrowing among large studies, and the Begg's funnel plot will show a symmetrical inverted funnel. If publication bias exists, the plot is asymmetrical or the p value is less than 0.05 by the Egger's test. We used Stata SE version 10.0 software package (StataCorp, College Station, Texas, USA) for the statistical analysis.

Results

Figure 1 shows a flow diagram for identifying relevant studies. A total of 293 articles were searched from two databases and hand-searching relevant bibliographies.

We excluded 32 duplicate articles and additional 208 articles not satisfying the selection criteria. We reviewed the full texts of the remaining 53 articles. Among them, 34 articles were excluded because of insufficient data (n = 15), irrelevant outcomes (n = 10), irrelevant study design (n = 6), identical trial (n = 2), and sharing participants with another study (n = 1). The remaining 20 studies (six cross-sectional studies, fiver case-control studies, and nine cohort studies) from 19 articles [11–25, 35–38] were included in the final analysis.

Study Characteristics

Table 1 summarizes the general characteristics of the 20 studies included in the final analysis. A total of 31,479 participants (8,398 in six cross-sectional studies, 4,601 in five case-control studies, and 19,918 in nine cohort studies) were included in the analysis. For studies reporting age and sex at the time of the enrollment period, the mean age of the study participants was 71.9 (range, 45 to 108 years), and 51.8% of them were women. The included studies were published from 1990 to 2014, spanning 24 years and were performed in the following countries: China (n = 3) [12, 13, 38], Finland (n = 2) [23, 24], Portugal (n = 2) [18, 25], USA (n = 3) [19, 21, 35], Australia (n = 1) [16], Canada (n = 1) [20], France (n = 1) [22], Norway (n = 1) [14], Taiwan (n = 1) [15], England (n = 1) [17], Japan (n = 2) [11, 37], and Jordan (n = 1) [36]. In cohort studies, follow-up periods ranged between 1.3 years and 28 years (mean, 8.4 years), and the completeness of follow-up ranged from 58.2 to 98.2% (mean, 75.8%). Regarding caffeine sources, five studies [18, 19, 22, 25, 35] presented an estimated amount of caffeine intake; eight studies [11, 12, 15, 16, 20, 23, 36, 37] presented both coffee and tea intake; five studies [13, 14, 17, 21, 38] presented only tea intake; and one study [24] presented only coffee intake. Highest categories of caffeine intake in each study ranged from more than 3 times per week to 8 cups per day as coffee units. Meanwhile, reference categories ranged from never or rare intake to 3 cups per day as coffee units.

Regarding diagnostic criteria of study outcomes, the included studies used DSM-IV [39] or TELE [40] for dementia, NINCDS-ADRDA [41] for AD, MMSE [42] for cognitive decline or cognitive impairment.

According to the quality assessment by the NOS, the mean value for the 14 case-control and cohort studies was 6.8 stars. In the current study, we considered a study awarded ≥7 stars as a high-quality study because the criteria for high quality have not been established. Among all the included studies assessed, eight studies [16, 18–22, 25, 38] were identified as having a high-quality (table 2).

Association of Caffeine Intake and Risk of Dementia

As shown in figure 2, caffeine intake was not significantly associated with the risk of cognitive disorders including dementia, AD, cognitive impairment, and cognitive decline in the random-effects meta-analysis of all 19 studies (OR/RR, 0.82; 95% CI, 0.67–1.01; $I^2 = 63.2$). In the subgroup meta-analysis by outcome, effect sizes (OR/RR with 95% CI) of caffeine intake were 0.72 (0.34–1.51) for dementia, 0.78 (0.50–1.22) for AD, 0.79 (0.61–1.04) for cognitive impairment, and 0.99 (0.70–1.39) for cognitive decline. No publication bias was observed in the included studies (Begg's funnel plot, symmetrical; Egger's test, p for bias = 0.63) (fig. 3).

Subgroup Meta-Analyses

Table 3 shows findings from the subgroup meta-analyses by various factors. Regarding the type of caffeine sources, the summary estimate for the association between coffee intake and cognitive disorders was 0.83 (95% CI, 0.70–0.98), with moderate heterogeneity (I^2 = 44.8%). However, in subgroup meta-analysis by study design, the summary estimates (RR or OR) of coffee intake for cognitive disorders were 0.70 (95% CI, 0.50–0.98; $I^2 = 42.0\%$) for cross-sectional study, 0.82 (95% CI, 0.55–1.24; $I^2 = 33.4\%$) for case-control study, and 0.90 (95% CI, 0.59–1.36; $I^2 = 60.0\%$) for cohort study. Also, no other significant association was observed in the remaining subgroup meta-analyses by the following factors: tea consumption, study design (cross-sectional vs. case-control vs. cohort), type of outcome (dementia vs. AD vs. cognitive impairment vs. cognitive decline), race of participants (Asian vs. Caucasian), gender (male vs. female), methodological quality (≥7 vs. <7), dosage of caffeine intake (lowest vs. moderate vs. highest), and caffeine intake whether daily or occasionally (coffee vs. tea).

Discussion

The current meta-analysis found that there was no association between caffeine intake from coffee or tea and the risk of cognitive disorders such as dementia, AD, cognitive impairment, and cognitive decline. Coffee intake was associated with a decreased risk of cognitive disorders in the meta-analysis of all the observational studies including cross-sectional, case-control, and cohort studies. However, in the subgroup meta-analysis of cohort studies, its preventive effect was not shown.

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Table 1. Characteristics of observational epidemiological studies included in the final analysis (n = 20)

	Study	Country	Follow-up period	Population (age, years)	Caffeine intake (highest vs. lowest)	Outcome measure	OR or RR (95% CI)	Adjustments
Cross-sectional studies (n = 6)								
1	Kuriyama (2006) [11]	Japan	n.a.	1,003 participants (≥70)	Coffee/Green tea: ≥2 cups/day vs. ≤3 cups/week	Cognitive impairment (MMSE score <26)	Coffee: 1.03 (0.59–1.80) Green tea: 0.46 (0.30–0.72) Black or oolong tea: 0.87 (0.55–1.38)	Age, sex, diabetes, hypertension, stroke, depressive symptom, education, visiting friends, energy intake, intake of nondietary vitamin C or E, and fish consumption
2	Ng (2008) [12]	China	n.a.	307 cases among 2,501 participants (≥55)	Coffee: ≥1 cup/day vs. never or rarely Tea: high (sum of green tea and black or oolong tea intake) vs. no drinking	Cognitive impairment (MMSE score ≤23)	Coffee: 0.99 (0.69–1.45) Tea: 0.37 (0.14–0.98)	Age, sex, education, smoking, alcohol consumption, BMI, hypertension, diabetes, heart disease, stroke, APOE ε4, physical activities, social and productive activities, vegetable and fruit consumption, fish consumption, tea (for coffee), and coffee (for tea)
3	Huang (2009) [13]	China	n.a.	95 male and 334 female cases among 681 participants (90–108)	Former or current tea consumption habit (almost every day) yes vs. no	Cognitive impairment (MMSE score <19)	Former: Male 0.92 (0.34–2.45) Female 0.86 (0.27–0.91) Current : Male 0.55 (0.22–1.64) Female 0.96 (0.38–2.45)	Age, sex, sleep habits, education level, religion habits, and temperament
4	Nurk (2009) [14]	Norway	n.a.	2,031 participants (70–74)	Habitual consumption of tea during the previous year vs. not	Cognitive impairment (m-MMSE score <10)	0.95 (0.68–1.33)	Sex, education, vitamin supplement, smoking, History of CVD, diabetes, and total energy intake
5	Wu (2011) [15]	Taiwan	n.a.	472 cases among 2,119 participants (≥65)	Coffee/tea: ≥1/week vs. no intake	Cognitive impairment (m-MMSE score <24)	Coffee: 0.51 (0.31–0.83) Tea: 0.99 (0.75–1.30)	Age, gender, education level, marital status, social support, hyperlipidemia, stroke, physical function, depressive symptoms, self-rated health, cigarette smoking, leisure-time physical activity, fruits and vegetables consumption, multivitamin intake, and BMI
6	Mashal (2013) [36]	Jordan	n.a.	63 participants (>60)	Coffee/tea intakes: yes/no	Cognitive impairment (MMSE score <24)	Coffee: 0.74 (0.3–1.6) Tea: 1.8 (1.1–2.8)	Serum total homocysteine
Case-control studies (n = 5)								
7	Broe (1990) [16]	Australia	n.a.	170 cases and 170 control (52–96)	Ever vs. never Coffee/tea: >4 cups/day vs. ≤4 cups/day	AD (NINCDS-ADRDA criteria)	Coffee: 0.65 (0.37–1.13) Tea: 0.50 (0.15–1.61) Coffee: 2.25 (0.72–7.71) Tea: 1.42 (0.93–2.17)	Age and sex (matching)

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Table 1. (continued)

Study		Country	Follow-up period	Population (age, years)	Caffeine intake (highest vs. lowest)	Outcome measure	OR or RR (95% CI)	Adjustments
8	Forster (1995) [17]	England	n.a.	109 cases and 109 controls (≤65)	Tea: >4 cups/day vs. ≤4 cups/day	AD (NINCDS-ADRDA criteria)	1.40 (0.81–2.63)	Age and sex (matching)
9	Maia (2002) [18]	Portugal	n.a.	54 case and 54 controls (≥50)	Caffeine exposure during the 20 years preceded diagnosis of AD vs. no exposure	AD (NINCDS-ADRDA criteria)	0.40 (0.25–0.67)	Age, sex (matching), hypertension, diabetes, stroke, head trauma, smoking habits, alcohol consumption, NSAID, vitamin E, gastric disorder, heart disease, education, and family history of AD
10	Gelber (2011) [19]	Japanese American men (USA)	n.a.	(nested case-control design from Honolulu Heart Program cohort study) 226 dementia cases among 3,494 participants (45–65) 118 AD cases 347 cases of cognitive impairment	Caffeine: ≥415.0 mg/day vs. 0–115.5 mg/day Coffee: ≥28 oz/day vs. 0 oz/day	Dementia (DSM III-R) AD (NINCDS-ADRDA criteria) Cognitive impairment (CASI score <74)	Dementia: Caffeine 1.12 (0.66–1.91) Coffee 1.09 (0.59–2.00) AD: Caffeine 0.95 (0.46–1.95) Coffee 0.59 (0.23–1.54) Cognitive impairment: Caffeine 1.02 (0.66–1.59) Coffee 0.99 (0.60–1.65)	Age, physical activity index, smoking, years of education, APOE ε4 status, elevated cholesterol, and hypertension
11	Boot (2013) [35]	USA	n.a.	147 cases and 294 controls (≥70)	Caffeine: ever vs. never	Dementia with Lewy bodies (DLB): dementia with 2 or more core features (fluctuations, parkinsonism, or visual hallucinations), or by one core feature plus one or more suggestive features (neuroleptic sensitivity, reduced dopamine uptake on functional imaging, or REM sleep behavior disorder)	Caffeine 0.29 (0.14–0.57)	Age and sex (matching)
Cohort studies (n = 9)								
12	Lindsay (2002) [20]	Canada	5 years (mean)	194 cases among 4,615 population-based random participants (≥65 years)	Coffee/tea: daily consumption vs. no	AD (screening with 3MS score <78/100 and NINCDS-ADRDA criteria)	Coffee: 0.69 (0.50–0.96) Tea: 1.12 (0.78–1.61)	Age, sex, and education
13	Dai (2006) [21]	Japanese American (USA)	6.3 years (mean)	63 cases among 1,589 participants (≥65)	Tea: ≥3/week vs. <1/week	AD (screening with CASI score <87 and NINCDS-ADRDA criteria)	Tea: 1.70 (0.67–4.33)	Gender, years of education, regular physical activity, BMI, baseline CASI score, olfaction diagnostic group, total energy intake, intake of fatty acids, APOE genotype, smoking, alcohol, supplementation of vitamin, fruit and vegetable juice drinking, dietary intake of vitamin C, vitamin E, and β-carotene

Table 1. (continued)

Study	Country	Follow-up period	Population (age, years)	Caffeine intake (highest vs. lowest)	Outcome measure	OR or RR (95% CI)	Adjustments
14 Ritchie (2007) [22]	France	3.47 years (mean)	7,017 participants (≥65)	Caffeine: >300 mg/day vs. 0–100 mg/day	Cognitive decline (ΔMMSE score ≤–2)	Male: 1.19 (0.89–1.59) Female: 0.91 (0.73–1.14)	Age, education, baseline cognitive performance, center
15 Ng (2008) [12]	China	1.3 years (mean)	461 cases among 1,438 participants (≥55)	Coffee: ≥1 cup/day vs. never or rarely Tea: high (sum of green tea and black or oolong tea intake) vs. no drinking	Cognitive decline (ΔMMSE score ≤–1)	Coffee: 1.07 (0.78–1.47) Tea: 0.57 (0.32–1.03)	age, sex, education, smoking, alcohol consumption, BMI (continuous), hypertension, diabetes, heart disease, stroke, depression, APOE _4, physical activities, social and productive activities, vegetable and fruit consumption, fish consumption, and coffee (for tea) and teas (for coffee)
16 Eskelinen (2009) [23]	Finland	21 years (mean)	61 cases among 1,409 participants (65–79) 48 cases among 1,409 participants (65–79)	Coffee: >5 cups/day vs. 0–2 cups/day Tea: ≥1 cup/day vs. no	Dementia (screening with MMSE score ≤24 and DSM-IV criteria) AD (screening with MMSE ≤24 and NINCDS-ADRDA criteria)	Dementia: Coffee 0.83 (0.32–2.15) Tea 1.04 (0.59–1.84) AD: Coffee 1.01 (0.33–3.08) Tea 0.91 (0.48–1.71)	Age, sex, education, follow-time, community of residence, midlife smoking, systolic blood pressure, serum total cholesterol, BMI, physical activity, APOE ε4, presence of late-life MI/stroke/diabetes, and Beck depressive scale
17 Laitala (2009) [24]	Finland	28 years (median)	445 cases among 2,606 twin participants (≥65) 642 cases among 2,606 participants (≥65)	Coffee: >8 cups/day vs. 0–3 cups/day	Dementia (TELE score <16) MCI (TELE score 16–17.5)	Dementia: 1.94 (0.86–4.38) MCI: 0.79 (0.38–1.66)	Education, age at interview, sex, alcohol, smoking, hypertension, hypercholesterolemia, diabetes, BMI, and cardiovascular disease
18 Santos (2010) [25]	Portugal	4 years (median)	531 participants (≥65)	Caffeine: >62 mg/day vs. <22 mg/day	Cognitive decline (ΔMMSE score ≤–2) Cognitive impairment (MMSE score ≤15 if they were illiterate, ≤22 if they had ≤11 years of education, ≤27 if they had >11 years of education)	Cognitive decline: Female 0.49 (0.24–0.97) Male 0.65 (0.27–1.54) Cognitive impairment: Female 0.10 (0.01–0.81) Male 1.53 (0.21–10.94)	Age, education, diabetes, smoking, and alcohol
19 Noguchi-Shinohara (2014) [37]	Japan	4.9 years (mean)	490 participants (>60)	Coffee: Everyday vs. none Green tea: Everyday vs. none	Dementia (DSM III-R) Cognitive decline (dementia or mild cognitive impairment)	Dementia: Coffee 0.70 (0.22–2.17) Green tea 0.26 (0.06–1.06) Cognitive decline: Coffee 1.16 (0.58–2.32) Green tea 0.32 (0.16–0.64)	Age, sex, history of hypertension, diabetes mellitus, hyperlipidemia, education, ApoE E4 carrier status, alcohol drinking, smoking, physical activities and/or hobbies.

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Table 1. (continued)

Study		Country	Follow-up period	Population (age, years)	Caffeine intake (highest vs. lowest)	Outcome measure	OR or RR (95% CI)	Adjustments
20	Wang (2014) [38]	China	2 years (mean)	223 participants (≥65)	Green tea: never vs. ever	Cognitive decline (ΔMMSE score ≤–2)	Cognitive decline: Green tea 2.08 (0.9–4.84)	Age and sex

MMSE = Mini-mental state examination; m-MMSE = a modified version of mini-mental state examination; BMI = body mass index; APOE = apolipoprotein; CVD = cardiovascular disease; AD = Alzheimer's disease; NINCDS-ADRDA = national institute of neurological and communicative disease and stroke-Alzheimer's disease and related disorders association; NSAID = non-steroidal anti-inflammatory drug; CASI = cognitive abilities screening instrument; 3MS = modified mini-mental state examination; DSM III-R = diagnostic and statistical manual of mental disorders, third edition, revised; DSM-IV = diagnostic and statistical manual of mental disorders, fourth edition; MI = myocardial infarction; TELE = telephone screening to identify potential dementia cases; MCI = mild cognitive impairment.

Table 2. Methodological quality of studies included in the final analysis based on the Newcastle-Ottawa Scale for assessing the quality of case-control studies and cohort studies (n = 14)

Case-control studies (n = 5)		Selection				Comparability	Exposure			Total (0–9)
		adequate definition of cases	representativeness of cases	selection of controls	definition of controls	control for important factor or additional factor	ascertainment of exposure (blinding)	same method of ascertainment for subjects	non-response rate*	
1	Broe (1990) [16]	☆	☆	☆	☆	☆	☆	☆	☆	8
2	Forster (1995) [17]	☆	☆	☆	☆	☆		☆		6
3	Maia (2002) [18]	☆	☆		☆	☆☆		☆	☆	7
4	Gelber (2011) [19]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
5	Boot (2013) [35]	☆	☆	☆	☆	☆		☆		6

Cohort studies (n = 9)		Selection				Comparability	Outcome			Total (0–9)
		representativeness of the exposed cohort	selection of the non exposed cohort	ascer-tainment of exposure	outcome of interest not present at start of study	control for important factor or additional factor	assessment of outcome	follow-up long enough for outcomes to occur	adequacy of follow-up of cohorts	
1	Lindsay (2002) [20]	☆	☆		☆	☆☆	☆	☆		7
2	Dai (2006) [21]	☆	☆		☆	☆☆	☆	☆		7
3	Ritchie (2007) [22]	☆	☆	☆	☆	☆☆	☆			7
4	Ng (2008) [12]	☆	☆		☆	☆☆	☆			6
5	Eskelinen (2009) [23]	☆	☆			☆☆	☆	☆		6
6	Laitala (2009) [24]	☆	☆			☆☆	☆	☆		6
7	Santos (2010) [25]	☆	☆	☆	☆	☆☆	☆			7
8	Noguchi-Shinohara (2014) [37]	☆	☆		☆	☆☆	☆			6
9	Wang (2014) [38]	☆	☆	☆	☆	☆	☆		☆	7

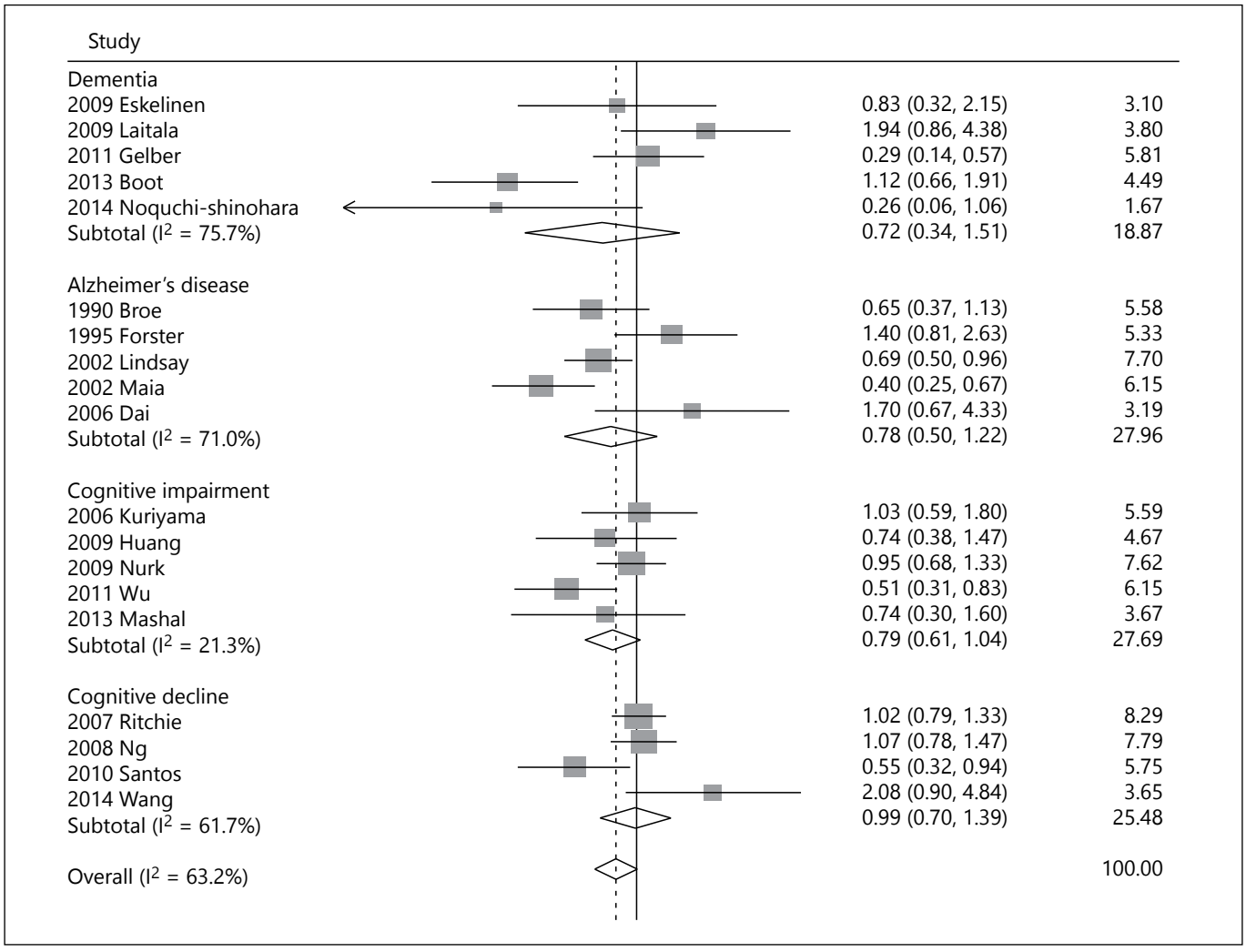

Fig. 2. Association between caffeine intake and cognitive disorders in the random-effects meta-analysis of epidemiological studies by type of outcomes.

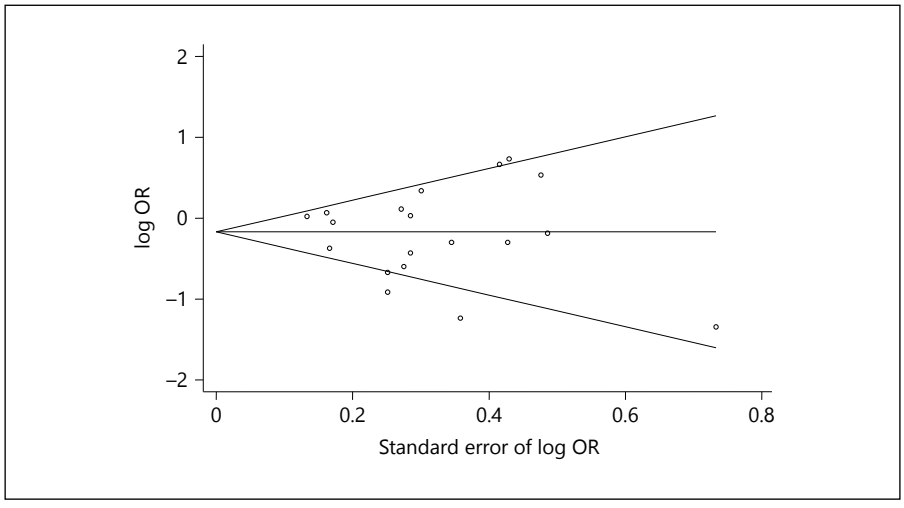

Fig. 3. Begg's funnel plot and Egger's test for identifying publication bias (n = 19).

Table 3. Association between caffeine intake from coffee or tea and the risk of cognitive disorders in subgroup meta-analyses

Category	No. of studies [reference number]	Summary OR/RR (95% CI)	Heterogeneity, I^2 (%)	Model used
Caffeine source				
Coffee	10 [11, 12, 15, 16, 19, 20, 23, 24, 36, 37]	0.83 (0.70–0.98)	44.8	Fixed-Effects
Cross-sectional study	3 [11, 15, 36]	0.70 (0.50–0.98)	42.0	Fixed-Effects
Case-control study	2 [16, 19]	0.82 (0.55–1.24)	33.4	Fixed-Effects
Cohort study	5 [12, 20, 23, 24, 37]	0.90 (0.59–1.36)	60.0	Random-Effects
Tea	13 [11–17, 20, 21, 23, 36–38]	1.00 (0.88–1.13)	40.5	Fixed-Effects
Cross-sectional study	5 [11, 13–15, 36]	1.02 (0.86–1.22)	44.6	Fixed-Effects
Case-control study	2 [16, 17]	0.96 (0.36–2.53)	56.9	Random-Effects
Cohort study	6 [12, 20, 21, 23, 37, 38]	1.04 (0.74–1.46)	50.2	Random-Effects
Study design				
Cross-sectional study	6 [11–15, 36]	–0.84 (0.68–1.05)	15.6	Fixed-Effects
Case-control study	5 [16–19, 35]	–0.66 (0.38–1.15)	79.3	Random-Effects
Cohort study	9 [12, 20–25, 37, 38]	0.96 (0.73–1.28)	58.8	Random-Effects
Case-control and cohort study	14 [12, 16–25, 35, 37, 38]	0.84 (0.64–1.10)	70.2	Random-Effects
Type of outcome				
Dementia (including AD)	10 [16–21, 23, 24, 35, 37]	0.77 (0.53–1.11)	70.6	Random-Effects
Dementia (excluding AD)	5 [19, 23, 24, 35, 37]	0.72 (0.34–1.51)	75.7	Random-Effects
Alzheimer's disease (AD)	7 [16–21, 23]	0.81 (0.57–1.15)	59.1	Random-Effects
Cognitive impairment	9 [11–15, 19, 24, 25, 36]	0.87 (0.73–1.03)	0	Fixed-Effects
Cognitive decline	5 [12, 22, 25, 37, 38]	1.01 (0.84–1.20)	50.0	Fixed-Effects
Race				
Asian (China, Taiwan, Japan, Japanease-American, Jordan, Japan)	9 [11, 12, 14, 15, 19, 21, 36–38]	0.94 (0.78–1.14)	49.8	Fixed-Effects
Caucasian (North America, Europe, Oceania)	10 [14, 16–18, 20, 22–25, 35]	0.75 (0.57–1.00)	71.0	Random-Effects
Gender				
Male	5 [12, 13, 19, 22, 25]	1.10 (0.89–1.38)	0	Fixed-Effects
Female	4 [12, 13, 22, 25]	0.90 (0.75–1.08)	12.3	Fixed-Effects
Methodological quality of the trials by NOS				
Among cohort studies				
High (≥7)	5 [20–22, 25, 38]	0.94 (0.64–1.37)	67.3	Random-Effects
Low (≤6)	4 [12, 13, 24, 37]	1.00 (0.58–1.73)	50.4	Random-Effects
Among case-control studies				
High (≥7)	3 [16, 18, 19]	0.66 (0.36–1.20)	74.2	Random-Effects
Low (≤6)	2 [17, 35]	0.65 (0.14–3.02)	91.2	Random-Effects
Among trials with both study designs				
High (≥7)	8 [16, 18–22, 25, 38]	0.82 (0.60–1.13)	69.7	Random-Effects
Low (≤6)	6 [12, 17, 23, 24, 35, 37]	0.83 (0.48–1.45)	74.1	Random-Effects
Dosage of caffeine intake[1]				
Lower	6 [11, 19, 22–25]	0.98 (0.81–1.19)	34.2	Fixed-Effects
Moderate	2 [19, 22]	1.11 (0.72–1.71)	69.7	Random-Effects
Highest	6 [11, 19, 22–25]	0.98 (0.87–1.10)	31.6	Fixed-Effects
Daily caffeine intake				
Coffee	3 [12, 20, 37]	0.77 (0.48–1.24)	67.7	Random-Effects
Tea	7 [12–14, 20, 21, 23, 37]	0.90 (0.76–1.07)	12.8	Fixed-Effects
Coffee or tea	7 [12–14, 20, 21, 23, 37]	0.90 (0.76–1.06)	33.5	Random-Effects

OR = Odds ratio; RR = relative risk; CI = confidence interval; NOS = Newcastle-Ottawa Scale.

[1] Highest intake was defined as quintile 5, quartile 4 or tertile 3; moderate as quintile 4 or quartile 3; lower as quintile 2, quartile 2, or tertile 2, respectively, based on each study's categorization.

The previous meta-analysis by Santos et al. [30] concluded that caffeine intake has an inverse association with cognitive impairment or decline. In addition, a quantitative review by Barranco Quintana in 2007 [29] showed that coffee consumption is inversely associated with the risk of AD from four observational studies. There are several hypotheses regarding the neuroprotective effect of coffee and tea. In addition to the biologic action of caffeine described in the introduction, coffee is rich in niacin, magnesium, and other antioxidant substances [43]. A main antioxidant in coffee is phenol chlorogenic acid (an ester of caffeic acid and quinic acid), which could carry neuroprotective properties against cognitive deterioration [44]. Also, some studies reported that coffee consumption lowers the risk of type 2 diabetes [45, 46]. Because insulin may have a role in normal cognitive functioning, and it regulates amyloid precursor protein (APP) and amyloid-β protein, insulin resistance may be associated with the pathophysiology of AD [46]. Besides, caffeine can act against neurodegenerative changes in the brain via positive effects on serum lipids [47, 48]. For another example, a recent observational study demonstrated that caffeine intake had a better cognitive maintenance in 2,475 elderly women with concomitant cardiovascular diseases or ≥3 coronary risk factors (i.e., diabetes, hypertension, hyperlipidemia, or obesity) [49].

As for tea, some animal studies [50, 51] suggested that tea has protective effects on cognitive function. There are also several ingredients in tea, which might affect cognitive function. Tea cathechins as antioxidants may reduce β-amyloid generation by promoting the cleavage of APP [52]. Besides, L-theanine, which is a major amino acid uniquely found in tea leaves may have a neuroprotective effect [53].

However, unlike the previous studies, our meta-analysis showed there was no association between caffeine intake and cognitive disorders. Especially, even though there was a significant preventive effect of coffee intake in the meta-analysis of all the included studies, its preventive effect was not observed in the subgroup meta-analysis of cohort studies or case-control studies; however, it was observed in the subgroup meta-analysis of cross-sectional studies. Given that a cohort study gives a higher level of evidence than a cross-sectional study or a case-control study, there is no clear evidence to support a beneficial effect of caffeine intake on cognitive disorders.

Our study has several limitations. First, we considered only coffee and tea as a source of caffeine intake. Therefore, there is a limitation regarding the generalization of our findings regarding the effect of caffeine intake on the risk cognitive disorders. Second, it was hard to evaluate the exact amounts of caffeine intake in each study. For example, the amount of caffeine contained in a cup of coffee ranges approximately from 71 to 220 mg according to the serving size, type of coffee bean, and preparation method [54]. In general, tea is classified into three types according to the degrees of fermentation: black tea (fully fermented), oolong tea (semi-fermented), and green tea (non-fermented). Ingredients such as total phenols, catechins, and caffeine of tea show significant variability according to those types [55]. Third, considerable heterogeneity in study designs, study outcomes, categories of caffeine intakes, and measures of cognitive disorders may preclude robust findings on this topic. For example, most studies had used very different cut-points of MMSE (ranged from 10 to 26 points) for measuring cognitive impairment. Last, our meta-analysis might create a biased measure of association in the findings because selection and recall biases are common in individual cross-sectional studies and case-control studies.

Nevertheless, the strength of our study is that we performed subgroup meta-analyses by various factors such as level of caffeine exposure, caffeine source, study design, study outcome, gender, and race of participants across studies to elicit a robust conclusion on this issue. Also, we examined a comprehensive meta-analysis including more cohort studies [37, 38], case-control studies [17, 19, 35] and cross-sectional studies [11, 13–15, 36] than the previous one.

Conclusion

In sum, our meta-analysis of observational epidemiological studies suggests that there is no association between caffeine intake from coffee or tea and the risk of cognitive disorders. Our findings should be confirmed by further large prospective cohort studies or if possible, studies with a higher level of evidence such as randomized controlled trials.

Disclosure Statement

The authors have nothing to disclose.

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