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Meta-analysis

Habitual coffee consumption and risk of cognitive decline/dementia: A systematic review and meta-analysis of prospective cohort studies

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ABSTRACT

Objective: Findings from epidemiologic studies of coffee consumption and risk for cognitive decline or dementia are inconclusive. The aim of this study was to conduct a meta-analysis of prospective studies to assess the association between coffee consumption and the risk for cognitive decline and dementia.

Methods: Relevant studies were identified by searching PubMed and Embase databases between 1966 and December 2014. Prospective cohorts that reported relative risk (RRs) and 95% confidence intervals (CIs) for the association of coffee consumption with dementia incidence or cognitive changing were eligible. Study-specific RRs were combined by using a random-effects model.

Results: Eleven prospective studies, including 29,155 participants, were included in the meta-analysis. The combined RR indicated that high coffee consumption was not associated with the different measures of cognitive decline or dementia (summary RR, 0.97; 95% CI, 0.84–1.11). Subgroup analyses suggested a significant inverse association between highest coffee consumption and the risk for Alzheimer disease (summary RR, 0.73; 95% CI, 0.55–0.97). The dose–response analysis, including eight studies, did not show an association between the increment of coffee intake and cognitive decline or dementia risk (an increment of 1 cup/d of coffee consumed; summary RR, 1.00; 95% CI, 0.98–1.02).

Conclusions: The present study suggests that higher coffee consumption is associated with reduced risk for Alzheimer disease. Further randomized controlled trials or well-designed cohort studies are needed to determine the association between coffee consumption and cognitive decline or dementia.

Introduction

Evidence from experimental studies of in vitro and preclinical animal models indicates that caffeine and other bioactive components of coffee may have plausible neuroprotective mechanisms on cognitive decline and dementia [1]. However, results from observational prospective studies, randomized controlled trials, and epidemiology of coffee consumption and cognitive decline or dementia risk were inconclusive. Some studies suggest a protective association, whereas others report no benefit. A systematic review and meta-analysis demonstrated a trend toward a protective

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effect of caffeine (including coffee) in cognitive decline or dementia [2]. In contrast, a recent meta-analysis of 247 cross-sectional and cohort studies of modifiable factors associated with cognition and dementia did not find an association between coffee intake and cognitive change [3]. To examine whether the association between coffee consumption and risk for cognitive decline or dementia varies by levels of coffee intake, a meta-analysis of prospective studies was performed. Whether the association varied by follow-up duration also was assessed because some studies indicated that the coffee protective association is observed only in the short term [4]. Additionally, whether the relation differed by dementia type, sex, and region of participation was examined.

Material and methods

Literature search and selection

Standard criteria were followed for performing and reporting meta-analyses of observational studies. A literature search was performed using PubMed and Embase databases that included the years 1966 through December 2014. We used the search terms *coffee* or *caffeine* combined with *dementia* or *Alzheimer disease* or *cognitive decline* or *cognitive impairment*. The search was limited to studies carried out in humans. Additionally, the coffee and dementia or Alzheimer disease of medical subject headings terms were used. Moreover, the reference lists of retrieved articles were scrutinized to identify further relevant studies. No language restrictions were imposed. Two researchers conducted all of the searches independently. A flowchart of the literature search is shown in Figure 1.

Studies were eligible for inclusion in this meta-analysis if they met the following criteria:

1. The study had a prospective design.
2. The exposure of interest was coffee consumption, including total coffee, decaffeinated coffee, or caffeinated coffee.
3. The outcome was cognitive decline or dementia or cognitive impairment; and
4. The investigators reported relative risks (RRs) with 95% confidence intervals (CIs).

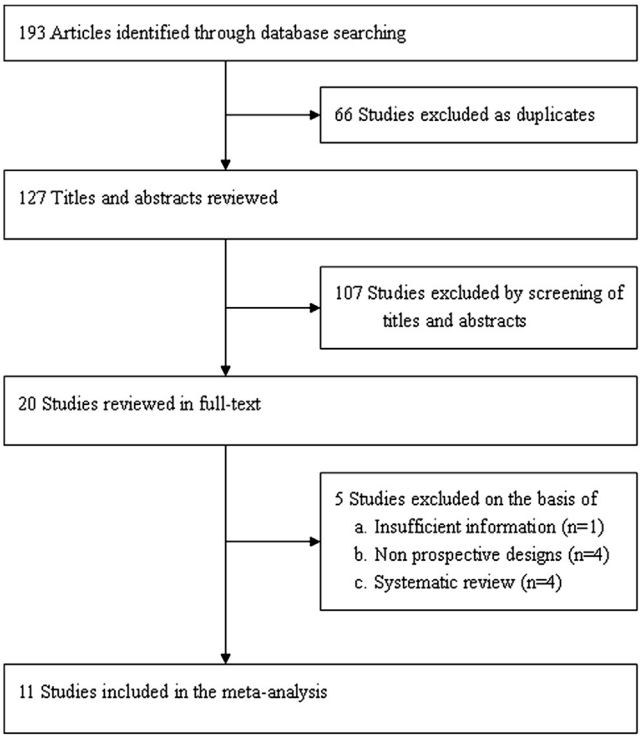

Fig. 1. Flowchart for identifying eligible studies.

If data were duplicated in more than one study, only the most recent and complete study was included.

Studies were grouped by the outcome addressed. Dementia and Alzheimer's disease were defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and/or National Institute of Neurologic and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association Criteria for Alzheimer's Disease (NINCDS-ADRDA) [2]. Cognitive decline was considered when studies quantified the difference in performance using neuropsychological instruments in two distinct occasions, regardless of cutoff values. An abnormal score in at least one of the tests, at any time, was defined as cognitive impairment [2].

Data extraction

For each included study, the first author's last name, year of publication, study location, sex, age, sample size (number of dementia cases or number of participants), duration of follow-up, RRs with 95% CIs for each category of coffee intake, and covariates adjusted for in the multivariable model were recorded. Study quality was evaluated by using the Downs and Black scoring system [5]. The risk estimates from the most fully adjusted multivariable model were extracted. Two researchers independently reviewed articles and extracted information.

For every study, the median or mean coffee consumption for each category was assigned to each corresponding RR. When the median or mean consumption per category was not reported in the article, the midpoint of the upper and lower boundaries in each category was assigned as the average consumption. If the upper boundary for the highest category was not provided, it was assumed that the boundary had the same amplitude as the adjacent category. When the lowest category was open-ended, the lower boundary was set to zero [2].

Statistical analysis

The measure of effect of interest was RR with corresponding 95% CI. Hazard ratio was considered as RR directly in some studies. Study-specific risk estimates were extracted from each article and log risk estimates were weighted by the inverse of their variances to obtain a pooled risk estimate. Studies were combined by using the DerSimonian and Laird random-effects model [6], which considers both within–and between-study variations. Study-specific estimates were calculated for highest versus lowest level of exposure category. In separate analyses, the RRs were grouped for comparable categories of coffee consumption as compared with the lowest category [7].

For dose–response analysis, previously proposed methods were used to estimate study-specific slopes from the natural logarithm of the RR across categories of exposure [8,9]. In studies that did not provide the number of cases and person-years in each exposure category, the variance-weighted least-square regression model was used to estimate the slopes [10]. Because the lower boundary of the lowest category or the upper boundary of the highest category was usually open, boundaries were considered in the same amplitude as the closest category. The summary RR estimates were obtained by grouping study-specific slopes, using the inverse of the corresponding variances as weights [7].

To examine heterogeneity among studies, the Q and I^2 statistics were used. Two cut points of these I^2 values were considered, creating three groups: <30% (no between-study heterogeneity or marginal between-study heterogeneity), 30%–75% (mild heterogeneity), and >75% (notable heterogeneity). Publication bias was evaluated with Egger's regression asymmetry test in which $P < 0.10$ was considered statistically significant [11]. Analyses stratified by sex, outcomes, study location, years of follow-up, and controlling ApoE $\varepsilon 4$ carrier status were conducted. Publication bias was evaluated with Egger's regression test. The present meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [12]. All statistical analyses were conducted with Stata software (StataCorp LP, College Station, TX, USA). $P < 0.05$ was considered statistically significant.

Results

Study characteristics

The literature search identified 127 articles, of which 116 were excluded after review of the title or abstract (Fig. 1). The remaining 11 articles [4,13–22] were based on data from

prospective studies and were eligible for inclusion in the meta-analysis. The studies were published from 2001 through 2014 (Table 1). Combined, these studies had 29,155 study participants. Nine studies were conducted in Europe and two in Asia. The studies included RR estimates that were adjusted for age (n = 11), education (n = 11), sex (n = 5), smoking (n = 8), alcohol consumption (n = 6), history of diabetes (n = 6), history of hypertension (n = 7), body mass index (n = 5), physical activity (n = 5), and ApoE ε4 carrier status (n = 4). The outcomes of the studies included cognitive decline (n = 4), cognitive impairment (n = 3), dementia (n = 5), Alzheimer disease (AD; n = 4), and vascular dementia (n = 1).

Overall and stratified association between coffee consumption and cognitive decline or dementia

A meta-analysis of the 11 studies suggested that high coffee consumption was not associated with the different measures of cognitive decline or dementia, with a summary RR of 0.97 (95% CI, 0.84–1.11), with no heterogeneity among the study results ($P = 0.14$, $I^2 = 24.9\%$; Fig. 2). The results of subgroup analyses stratified by various study and participant characteristics are shown in Table 2. When the analysis was stratified by outcomes, it was noted that coffee intake was significantly associated with a decreased risk for AD (summary RR, 0.73; 95% CI, 0.55–0.97), whereas no significant results were apparent in the cognitive decline (summary RR, 1.02; 95% CI, 0.88–1.18), cognitive impairment (summary RR, 0.78; 95% CI, 0.48–1.26), or dementia (summary RR, 1.08; 95% CI, 0.81–1.44). When it was conducted by sex, no significant association was observed in either men (summary RR, 1.15; 95% CI, 0.90, 1.48) or women (summary RR, 079; 95% CI, 0.87–1.11). When the analysis was stratified by geographic region, no significant results were apparent either in the European (summary RR, 0.96; 95% CI, 0.81–1.12) or in the Asian countries (summary RR, 1.06; 95% CI, 0.80–1.40). When subgroup analysis was conducted by year of follow-up, no evidence of a protective association was found between higher coffee consumption and incidence of cognitive decline or dementia, either among studies with a shorter follow-up (summary RR, 0.88; 95% CI, 0.69–1.11) or those with a longer follow-up (summary RR, 1.02; 95% CI, 0.86–1.22). When stratified by ApoE ε4 carrier status, no significant association between coffee consumption and cognitive decline or dementia risk was observed either among studies controlling ApoE ε4 carrier status (summary RR, 1.04; 95% CI, 0.84–1.11) or those without (summary RR, 0.94; 95% CI, 0.77–1.15). Sensitivity analysis showed that the risk for cognitive decline or dementia did not vary substantially with the exclusion of any individual study. There was little evidence of significant publication bias, as indicated by the Egger linear regression test ($P = 0.80$).

Dose–response analysis

Eight studies were included in the dose–response analysis (Fig. 3), which showed an association between coffee intake and the different measures of cognitive decline or dementia (an increment of 1 cup/d of coffee consumed; summary RR, 1.00; 95% CI, 0.98–1.02; P for heterogeneity = 0.27; $I^2 = 16\%$). The summary RR of cognitive decline for an increase of 1 cup/d of coffee consumed was 0.99 (95% CI, 0.94–1.03). For cognitive impairment, the combined relative risk for an increase of 1 cup/d of coffee consumed was 0.97 (95% CI, 0.90–1.02). For dementia, the combined relative risk for an increase of 1 cup/d of coffee consumed was 1.01 (95% CI, 0.98–1.05). For AD, the combined relative risk for an increase of 1 cup/d of coffee consumed was 1.02 (95% CI, 0.95–1.08).

Discussion

Findings from this meta-analysis of prospective studies indicated that dietary coffee consumption may not be associated with the different measures of cognitive decline or dementia. The result of dose–response analysis also did not show an association between the increment of coffee intake and different measures of cognitive decline or dementia. However, in the subgroup analysis, a statistically significant 27% reduction in risk for AD was observed in the highest category of coffee consumption compared with the lowest.

Several epidemiologic studies have shown a negative association between coffee drinking and cognitive decline or dementia risk. An early quantitative review of two case–control and two cohort studies published in January 2004 suggests a negative association between coffee consumption and AD (RR, 0.73; 95% CI, 0.58–0.92), despite important heterogeneity in methods and results [1]. An updated meta-analysis [2] that included two case–control and nine cohort studies published in September 2009, also demonstrated a trend toward a protective effect of caffeine (including coffee) in cognitive decline dementia (RR, 0.84; 95% CI, 0.72–0.99). When considering only the cohort studies, the summary RR was 0.93 (95% CI, 0.83–1.04). The summary RR was 0.83 (95% CI, 0.32–2.15) for AD, although it combines estimates from two case–control and two cohort studies. In the current meta-analysis, 11 prospective studies were reviewed and no association between coffee intake and the different measures of cognitive decline or dementia (summary RR, 0.97; 95% CI, 0.84–1.11) was found. However, it was noted that coffee intake was significantly associated with a decreased risk for AD (summary RR, 0.73; 95% CI, 0.55–0.97) when the analysis was stratified by outcomes. The large methodologic heterogeneity across a still limited number of reports could partly account for the different results among the studies. Compared with the case–control study, studies included in this meta-analysis were prospective design, which minimized the possibility of recall and selection biases. The present study was able to enhance the precision of the risk estimates that might not be evident in a single study; we also conducted subgroup analyses to explore the potential sources of heterogeneity, thereby increasing the clinical relevance of findings. Studies concerning other common sources of caffeine, in addition to coffee, including tea, soft drinks, and energy drinks, and chocolate derived from cocoa beans, were not reviewed in the present study. Moreover, coffee is a complex mixture containing not only caffeine, but various bioavailable polyphenols such as chlorogenic acid that may act via numerous mechanisms to produce the beneficial effects seen in cognitive function or dementia [23]. Therefore, creating defined categories and types of exposure might be useful in conducting meta-analyses and may increase statistical power for the detection of an association between coffee and cognitive decline and dementia [2].

It is biologically plausible that coffee consumption might have a protective effect on risk for AD. Coffee is a complex mixture of biologically active substances that may have both beneficial and harmful effects on the central nervous system. A potential mechanism for the neuroprotective effect of coffee may involve blockade adenosine receptor antagonism, which may attenuate damage caused by β-amyloid, the toxic peptide that accumulates in the brain of patients with AD [24]. Findings from one study demonstrated that moderate caffeine intake (the human

Table 1
Characteristics of observational prospective studies of coffee consumption and cognitive decline or dementia

First author, year [reference]	Country and study period	Mean duration of follow-up, y	Sex, age range, y	Sample size	Outcomes, case (n)	Cognitive function assessment	Coffee consumption	Adjusted RR	95% CI	Adjustment factor
Tyas, 2001 [13]	Canada 1991–1997	5	Both, 65–93	694	AD, 36	MMSE, NINCDS-A,DRDA	Nonregular	1.0	Reference	Age, sex, education
							Regular (nearly every day)	1.03	0.47–2.28	
Lindsay, 2002 [14]	Canada 1991–1996	5	Both, ≥65	4615	AD, 194	MMSE, NINCDS-A,DRDA	Not daily	1.0	reference	Age, sex, education
							Daily	0.69	0.50–0.96	
Ritchie, 2007 [15]	France 1999–2001	3.47	Both, ≥65	7017	Cognitive decline	MMSE, Benton test, DSM-IV	ΔMMSE ≤−2			Age, education, baseline cognitive performance and center
							Male			
							None	1.0	Reference	
							1–2 cup/d	1.02	0.81–1.28	
							2–3 cup/d	1.00	0.79–1.27	
							>3 cup/d	1.19	0.89–1.59	
							Female			
							None	1.0	Reference	
							1–2 cup/d	0.97	0.81–1.17	
							2–3 cup/d	0.89	0.72–1.08	
							>3 cups/d	0.91	0.73–1.14	
Ng, 2008 [16]	Singapore 2003–2007	1.3	Both, ≥55	1438	Cognitive decline/impairment	MMSE	Whole sample			Age, sex, education, smoking, alcohol consumption, BMI, hypertension, diabetes, heart disease, stroke, depression, ApoE ε4, physical activities, social and productive activities, vegetable and fruit consumption, fish consumption, and teas
							Never or rarely	1.0	Reference	
							Occasionally	1.01	0.64–1.60	
							>1 cup/d	1.07	0.78–1.47	
							Male			
							Never or rarely	1.0	Reference	
							Occasionally	1.13	0.49–2.62	
							>1 cup/d	1.31	0.71–2.44	
							Female			
							Never or rarely	1.0	Reference	
							Occasionally	0.97	0.55–1.71	
							>1 cup/d	1.03	0.70–1.51	
Eskelinen, 2009 [17]	Finland 1972–1998	21	Both, 65–79	1409	Dementia, 61; AD, 48	MMSE, DSM-IV	Dementia			Age, sex, education, follow-up time, smoking, systolic blood pressure, serum total cholesterol, BMI, physical activity, ApoE ε4, myocardial infarction, stroke, diabetes mellitus, Beck depressive scale,
							0–2 cups/d	1.0	Reference	
							3–5 cups/d	0.30	0.10–0.93	
							>5 cups/d	0.83	0.32–2.15	
							AD			
							0–2 cups/d	1.0	Reference	
							3–5 cups/d	0.42	0.12–1.46	
							>5 cups/d	1.01	0.33–3.08	
Laitala, 2009 [18]	Finland 1958–1986	28	Both, ≥65	2606	Cognitive impairment/ dementia dementia, 445	TELE, TICS	TELE			education, age at the interview, sex, BMI, binge drinking, smoking, life satisfaction, cardiovascular disease, hypercholesterolemia, hypertension, and diabetes
							Dementia			
							0–3 cups/d	1.0	Reference	
							3.5–8 cups/d	0.91	0.52–1.58	
							>8 cups/d	1.94	0.86–4.38	
					MCI, 642		MCI			
							0–3 cups/d	1.0	Reference	
							3.5–8 cups/d	0.83	0.54–1.27	
							>8 cups/d	0.79	0.38–1.66	
							TICS			

(*Continued*)

Table 1 (*Continued*)

First author, year [reference]	Country and study period	Mean duration of follow-up, y	Sex, age range, y	Sample size	Outcomes, case (n)	Cognitive function assessment	Coffee consumption	Adjusted RR	95% CI	Adjustment factor
					Dementia, 345		Dementia			
							0–3 cups/d	1.0	Reference	
							3.5–8 cups/d	1.27	0.69–2.34	
							>8 cups/d	2.27	0.88–5.82	
					MCI, 637		MCI			
							0–3 cups/d	1.0	Reference	
							3.5–8 cups/d	1.29	0.83–1.99	
							>8 cups/d	1.33	0.65–2.74	
Santos, 2010 [19]	Portugal 1999–2008	4	Both, ≥18	309	Cognitive decline/ impairment	MMSE	Cognitive decline (ΔMMSE ≤−2)			Age, education, BMI, diabetes, hypertension, smoking, alcohol drinking
							Male			
							<22 mg/d	1.0	Reference	
							22–62 mg/d	0.91	0.43–1.91	
							>62 mg/d	0.65	0.27–1.54	
							Female			
							<22 mg/d	1.0	Reference	
							22–62 mg/d	0.65	0.37–1.17	
							>62 mg/d	0.49	0.24–0.97	
							Cognitive impairment			
							Male			
							<22 mg/d	1.0	Reference	
							22–62 mg/d	NS	NS	
							>62 mg/d	1.53	0.21–10.94	
							Female			
							<22 mg/d	1.0	Reference	
							22–62 mg/d	0.54	0.19–1.59	
							>62 mg/d	0.10	0.01–0.81	
Gelber, 2011 [20]	USA 1965–1993	28	Male 71–93	3734	Clinical dementia and cognitive impairment	CASI, MMSE, DSM III-R	All dementia			Age, physical activity index, smoking, years of education, ApoE ε4, elevated cholesterol, and hypertension
							0 oz/d	1	Reference	
							4–8 oz/d	0.93	0.59–1.46	
							12–16 oz/d	1.24	0.78–1.97	
							20–24 oz/d	1.14	0.66–1.98	
							≥28 oz/d	1.09	0.59–2.00	
							AD			
							0 oz/d	1	Reference	
							4–8 oz/d	0.89	0.50–1.59	
							12–16 oz/d	1.09	0.60–2.00	
							20–24 oz/d	0.95	0.45–2.00	
							≥28 oz/d	0.59	0.23–1.54	
							Vascular dementia			
							0 oz/d	1	Reference	
							4–8 oz/d	1.37	0.64–2.94	
							12–16 oz/d	1.54	0.69–3.41	
							20–24 oz/d	1.57	0.62–3.95	
							≥28 oz/d	1.96	0.76–5.03	
							Cognitive impairment (CASI <74)			
							0 oz/d	1	Reference	
							4–8 oz/d	1.08	0.74–1.57	
							12–16 oz/d	1.07	0.72–1.59	
							20–24 oz/d	1.18	0.75–1.87	
							≥28 oz/d	0.99	0.60–1.65	

Vercambre, 2013 [21]	France 1995–2005	10	Female ≥65	2475	Cognitive decline	TICS	None	1	Reference	Marital status, alcohol intake, physical activity, use of multivitamin supplements, smoking status, BMI, postmenopausal hormone therapy use, aspirin use, history of depression
							≥4 cups/d	0.02	0.00–0.05	
Mirza, 2014 [4]	Netherlands 1989–2011	13.2	Both	4368	Dementia	MMSE	Stratum 0–4 y			Age, sex, education level, family history of dementia, working status, BMI, smoking, diabetes, hypertension, and alcohol use
							0–1 cup/d	1	Reference	
							1–3 cups/d	0.87	0.55–1.37	
							3 cups/d	0.69	0.42–1.15	
							Stratum >4 y			
							0–1 cup/d	1	Reference	
							1–3 cups/d	0.85	0.62–1.17	
							3 cups/d	1.14	0.83–1.56	
Noguchi-Shinohara, 2014 [22]	Japan 2007–2013	6	Both, ≥60	490	Cognitive decline/ dementia	MMSE, CDR	Dementia			Age, sex, history of hypertension, diabetes mellitus, hyperlipidemia, education, and ApoE ε4, alcohol drinking, smoking, physical activities and/or hobbies, and coffee and black tea consumption
							None	1	Reference	
							1–6 d/wk	1.00	0.34–2.99	
							Daily	0.70	0.22–2.17	
							Cognitive decline			
							None	1	Reference	
							1–6 d/wk	1.26	0.62–2.54	
							Daily	1.16	0.58–2.32	

AD, Alzheimer's disease; BMI, body mass index; CASI, Cognitive Abilities Screening Instrument; CDR, Clinical Dementia Rating; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NINCDS-ADRDA, National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Criteria for Alzheimer's Disease; TELE, Telephone assessment for dementia; TICS, Telephone Interview for Cognitive Status

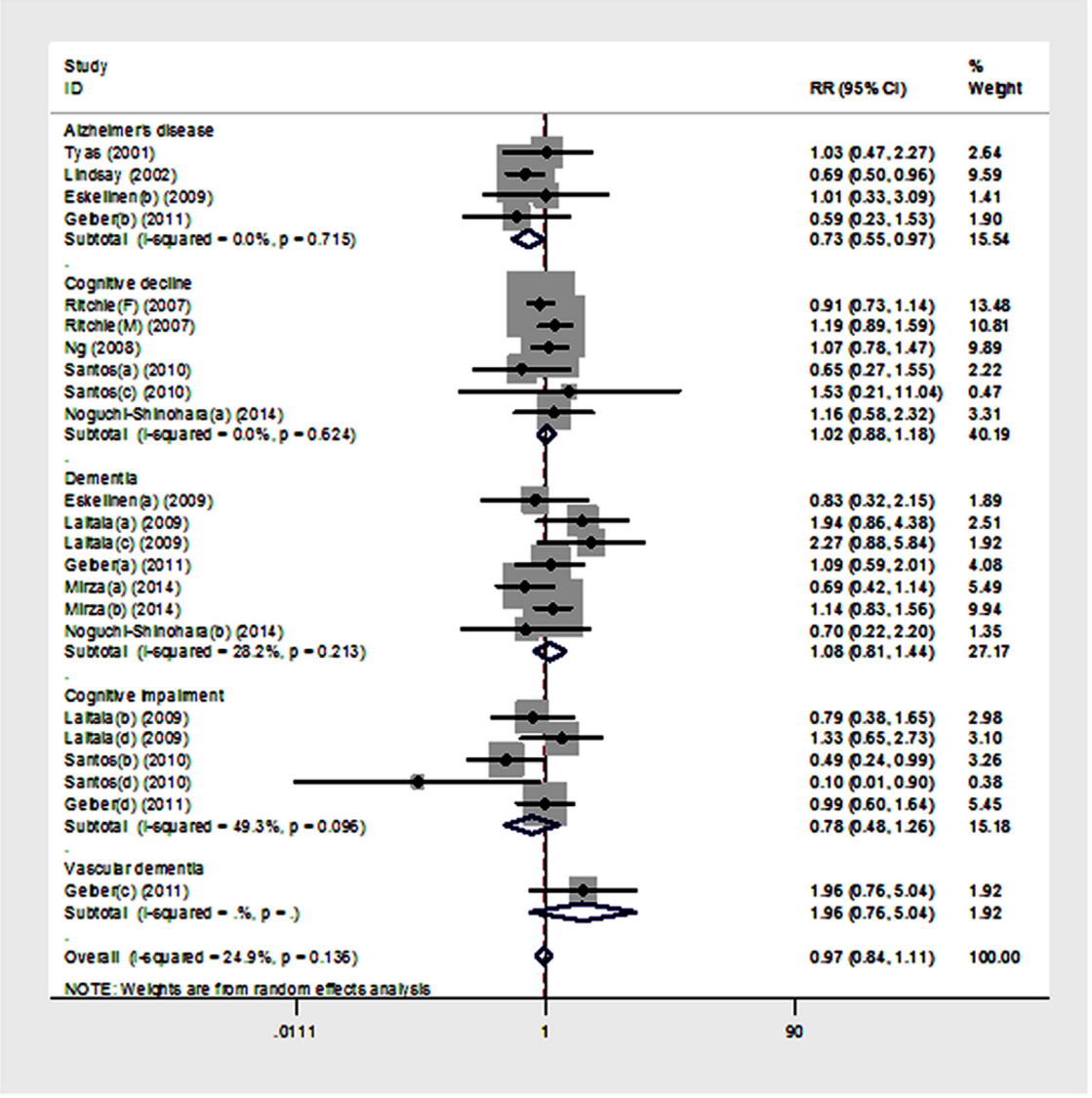

Fig. 2. Summary relative risks for cognitive decline or dementia comparing highest with lowest coffee consumption.

equivalent of 500 mg caffeine or 5 cups/d of coffee) could protect against or treat AD in an AD mouse model [25]. Moreover, habitual coffee consumption has been associated with higher insulin sensitivity and reducing the risk for diabetes, which is a strong risk factor for cognitive decline; this pathway would be particularly more relevant in populations with cognitive impairment [21].

Several potential limitations must be considered when interpreting the results. First, because multiple measurements of cognitive functioning or dementia were available, studies of present meta-analysis, screening by the Mini Mental State Examination, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, telephone assessment for dementia, or Clinical Dementia Rating were able to investigate associations for cognitive decline, cognitive impairment, and dementia. The results of the present study showed that coffee consumption is not significantly related to cognitive decline or dementia but is significantly related to AD. This finding emphasizes the importance of repeated measures of cognitive functioning, including a more extensive battery of cognitive tests to obtain information about different cognitive domains. Second, assessing the relation between duration of exposure to caffeine and cognitive decline or dementia, and the timing of exposure evaluation also is a source of heterogeneity across studies [4]. Coffee intake habits may decrease with time as cognitive impairment occurs, and a protective effect of caffeine was more likely in studies with shorter follow-up [2]. One study found a protective association between coffee consumption and dementia only in the follow-up stratum of 0 to 4 y [4]. In the Three City Study [15], consuming more than 3 cups/d of a caffeinated beverage (coffee or black tea) was associated with a lower decline in cognitive tests among elderly women, but there was no relationship between caffeine consumption and dementia risk over a 4-y period. The same result was found in a Japanese population [22]. The relatively short follow-up period and the small sample size might partly explain why there were no identified protective effects of coffee against cognitive decline or dementia [22]. Finally, as a meta-analysis of observational studies, the possibility that other factors may account for the

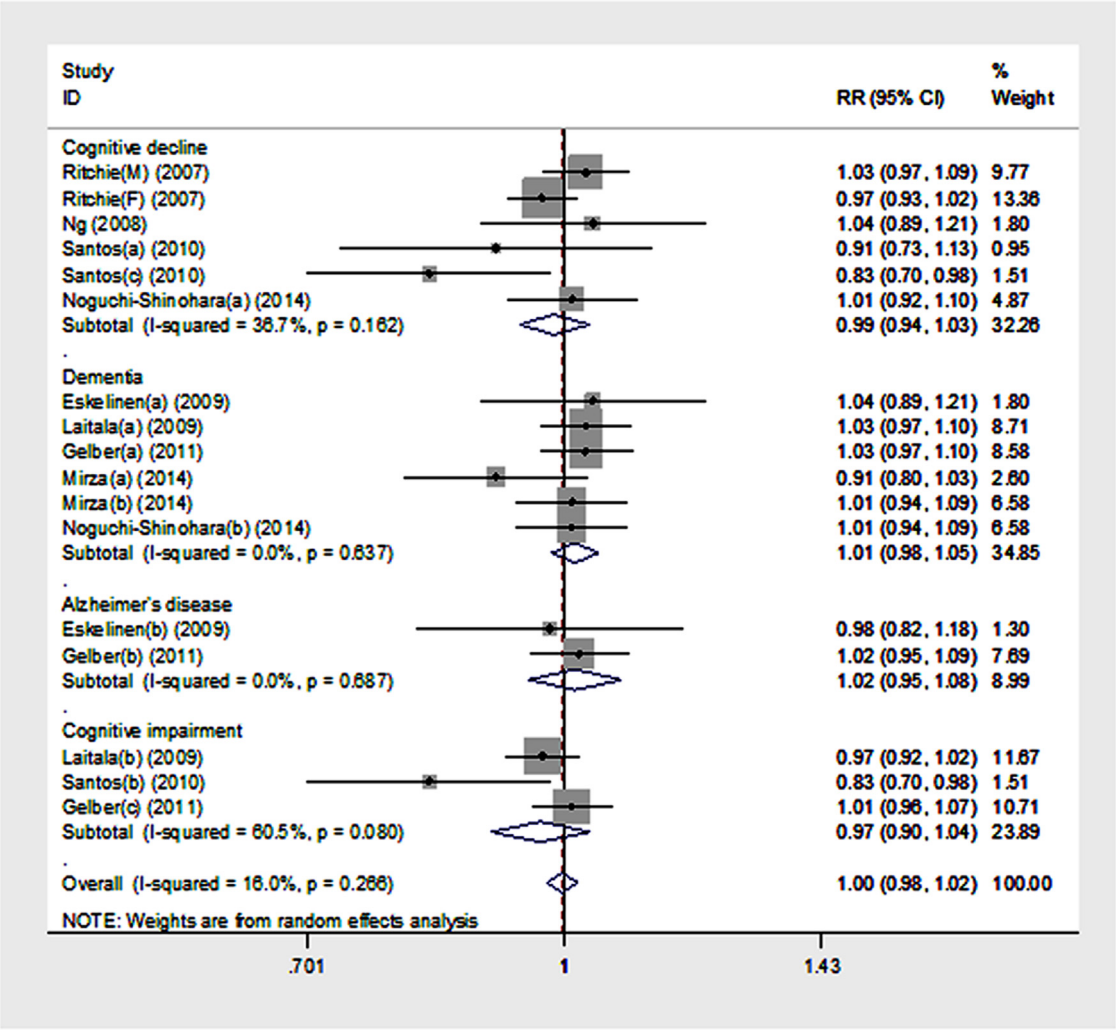

Fig. 3. Summary relative risks for cognitive decline or dementia for an increase in coffee consumption of 1 cup/d.

Table 2
Stratified summary RRs for the highest versus the lowest category of coffee consumption to cognitive decline or dementia risk

Group	No. of cohorts	RR (95% CI)	Q statistic	*P*-value	I^2-value (%)
Outcomes					
Cognitive decline	4	1.02 (0.88–1.18)	3.50	0.62	0.0
Cognitive impairment	3	0.78 (0.48–1.26)	7.89	0.10	49.3
Dementia	5	1.08 (0.81–1.44)	8.36	0.21	28.2
Alzheimer disease	4	0.73 (0.55–0.97)	1.36	0.72	0.0
Vascular dementia	1	1.96 (0.76–5.04)	0	NS	NS
Sex					
Male	3	1.15 (0.90–1.48)	1.95	0.58	0
Female	3	0.79 (0.87–1.11)	7.19	0.07	58.3
Geographic region					
Europe	9	0.96 (0.81–1.12)	28.29	0.08	32.8
Asia	2	1.06 (0.80–1.40)	0.57	0.75	0
Duration of follow-up, y					
≤4	4	0.88 (0.69–1.11)	15.98	0.07	46
>4y	7	1.02 (0.86–1.22)	12.97	0.31	12.4
Controlling ApoE ε4 carrier status					
Yes	4	1.04 (0.84–1.11)	3.96	0.14	24.9
No	7	0.94 (0.77–1.15)	24.76	0.03	47.5

observed associations, such as hypertension or diabetes, that in themselves enforce the risk for cognitive decline or dementia, cannot be excluded. Indeed, this can be observed when adjusted and unadjusted effect sizes are compared in the studies included in the meta-analysis, although an inverse relation [17,19] and no effects are shown in other studies [14,20]. This might be due to the studies' heterogeneity of the selected confounders and the effects of additional factors such as the ApoE allele. In the present meta-analysis, most of studies adjusted the influence of ApoE ε4 carrier status; some of them demonstrated that family history of dementia was not associated with AD, whereas an increased risk for AD was observed for individuals who had the APOE ε4 allele [14,17]. Thus, caution should be exercised in interpreting the results.

Conclusion

The present meta-analysis of prospective cohorts suggests that higher coffee consumption is associated with reduced risk for AD. Randomized controlled trials or well-designed cohort

studies are needed to determine the association between coffee and cognitive decline or dementia.

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