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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).

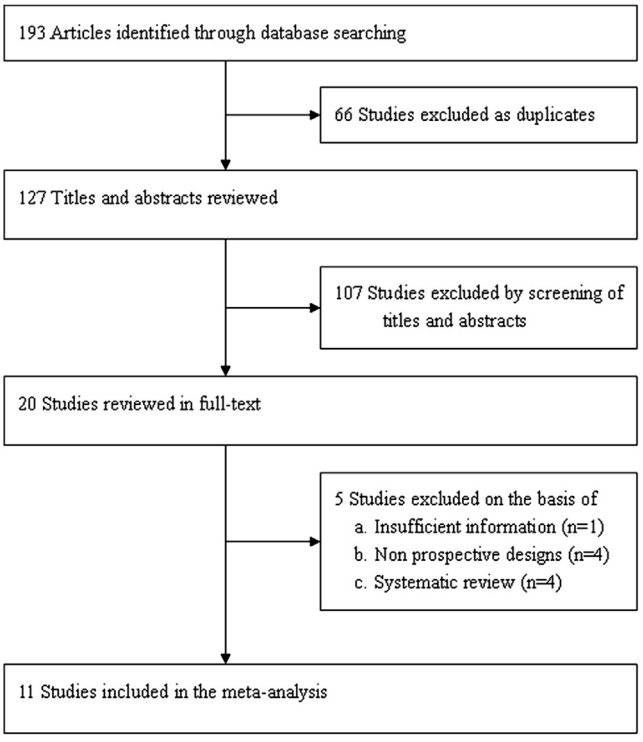

Fig. 1. Flowchart for identifying eligible studies.

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