Dement Neurocogn Disord. 2020 Sep;19(3):108-113
https://doi.org/10.12779/dnd.2020.19.3.108
pISSN 1738-1495·eISSN 2384-0757

DND Dementia and Neurocognitive Disorder

Original Article

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History of Coffee Consumption and Risk of Alzheimer's Disease: a Meta-epidemiological Study of Population-based Cohort Studies

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OPEN ACCESS

Received: Jun 4, 2020
Revised: Jul 29, 2020
Accepted: Aug 17, 2020

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Funding
This work was supported by the 2020 education, research and student guidance grant funded by Jeju National University.

Conflict of Interest
The author has no financial conflicts of interest.

ABSTRACT

Background and Purpose: Four published quantitative systematic reviews showed conflicting results involving coffee consumption and the risk of Alzheimer's disease (AD). The aim of this meta-epidemiological meta-analysis (MEMA) was to evaluate the factors underlying the conflicting results and estimate the effect size and direction of the AD risk associated with coffee consumption in population-based cohort studies.
Methods: The primary subjects of MEMA were derived from 3 cohort studies selected by the related systematic reviews. Additional studies involving the primary subjects were searched using citation discovery tools. Prospective cohort studies evaluating the association between coffee consumption and AD risk were selected. A fixed effects model was applied to estimate the summary relative risk (sRR) and its 95% confidence intervals (CIs). Subgroup analysis was conducted according to the level of coffee consumption. Egger's test was used to evaluate publication bias.
Results: Four cohort studies were finally selected. A total of 36,300 participants from Finland, Sweden, Germany, and the United States of America were selected. The sRR (and its 95% CI) (I-squared value) by highest-versus-lowest method was 0.98 (0.92–1.05) (0.0%). In addition, none of the results of subgroup analyses by the level of coffee consumption showed any statistical significance.
Conclusions: This MEMA found that there was no association between coffee consumption and AD risk. Based on recent evidence suggesting that gene-environment interactions contribute to AD pathogenesis, it is necessary to conduct population-based cohort studies involving non-Caucasians.

Keywords: Coffee; Alzheimer Disease; Cohort Studies; Meta-analysis

INTRODUCTION

The disease burden associated with age-related neurodegenerative disorders is increasing along with the increase in human lifespan.[1] Dementia is the leading cause of disability in the elderly, and Alzheimer's disease (AD) accounts for the most substantial portion of dementia.[2]

Drugs and diet are modifiable risk factors for AD development.[3] It has been argued that coffee consumption prevents AD via a biochemical mechanism of action.[4,5] However, quantitative systematic reviews of observational epidemiological studies to evaluate the association between coffee consumption and AD occurrence did not show consistent results (**Table 1**). The conflicting findings may be attributed to the following 3 factors. First, it might be related to a difference in selection criteria for the research design. Three systematic reviews,[6-8] including nested case-control studies as well as prospective cohort studies, suggested that coffee consumption had the effect of preventing AD occurrence. However, Larsson and Orsini,[9] which selected only cohort studies, showed no statistical significance. Second, it might be related to a difference in the selection criteria, because 2 of the 5 cohort studies selected in Larsson and Orsini[9] had AD death as the outcome.[10,11] Finally, it might be associated with a difference in the unit selection of coffee consumption because results differed with the application of the highest versus lowest method (HLM), which utilized the results of the highest consumption group based on the lowest group, and the dose-response meta-analysis based on cups of coffee consumption per day (cup/d).

Thus, it is necessary to select only population-based cohort studies with AD occurrence as the outcome, followed by a new meta-analysis according to the amount of coffee consumption. A meta-epidemiological study for previous systematic reviews was conducted to evaluate the association between coffee consumption and AD.[12,13]

METHODS

The meta-epidemiological study involved articles selected by the reported systematic reviews.[12,13]Among the articles selected from the 4 systematic reviews presented in **Table 1**, a total of 3 cohort studies analyzed the incidence of AD according to coffee consumption.[14-16]

Of the 3 cohort studies selected from the previous systematic reviews, the most recent presentation year was 2018.[16] Therfore, any study reported untill April 20, 2020 should be searched. To this end, the citation discovery tool of 'cited by' provided by PubMed was used to create a list of articles citing the cohort studies selected by the systematic reviews shown in **Table 1**.[17] Next, the articles were selected if the population-based prospective cohort study showed the magnitude of AD risk according to coffee consumption.

The relative risks (RRs) and 95% confidence intervals (CIs) adjusted for confounding factors were extracted from the articles finally selected. Finally, the logarithmic RR and standard error of logarithm RR were calculated. To determine the effect size by the level of coffee intake, the coffee intake was categorized into low (0–2 cup/d), moderate (3–5 cup/d), and high (more than 6 cups/d) groups.[18] The level of heterogeneity was assessed as I-squared

Table 1. sRR and 95% CIs of the published systematic reviews involving population-based cohort studies

Authors	Year of publication	Searching	Intake	Selected studies	sRR (95% CI)	I-squared (%)
Barranco Quintana et al.[6]	2007	Jan 2004	-	2NC	0.73 (0.54–0.99)	-
Liu et al.[7]	2016	Dec 2014	HLM	2CO+2NC	0.73 (0.55–0.97)	0.0
			1 cup/d	2CO	1.02 (0.95–1.08)	0.0
Wu et al.[8]	2017	Feb 2016	1–2 vs. 0 cup/d	2CO+1NC	0.71 (0.54–0.94)	0.0
			3< vs. 0 cup/d	2CO	1.07 (0.63–1.82)	0.0
Larsson and Orsini[9]	2018	Oct 2018	1 cup/d	5CO (2 mortality)	1.01 (0.95–1.07)	41.8

sRR: summary relative risk, CI: confidence interval, NC: nested case-control study, HLM: highest versus lowest method, CO: cohort study, cup/d: cup per day.

https://doi.org/10.12779/dnd.2020.19.3.108

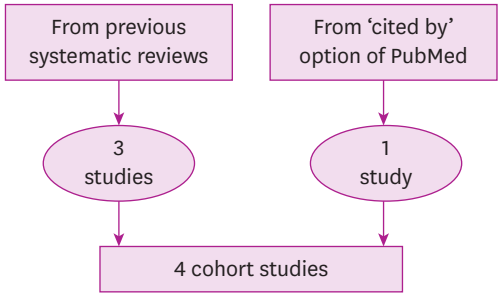

Fig. 1. Flow-chart of the final selection of prospective cohort studies.

value (%) and, if less than 50%, a fixed-effect model was used to calculate the summary RR (sRR) and its 95% CI.[19] Egger's test was performed to identify publication bias,[20] and the *p* value for statistical significance was 0.05.

RESULTS

A total of 388 articles cited 5 studies selected from 4 systematic reviews in **Table 1** as of April 30, 2020.[14-16,21,22] A new study was selected using the selection criteria.[23] Therefore, 4 cohort studies were finally selected for meta-analysis (**Fig. 1**).[14-16,23] The studies reported from Northern Europe (Finland, Sweden, Germany) and North America (USA) involved a total of 36,300 participants. Three studies[14,15,23] reported the RRs adjusted for apolipoprotein Eε4 carrier status.

The effect size based on HLM from the 4 cohort studies showed no statistical significance (sRR=0.98; 95% CI, 0.92–1.05) with no heterogeneity between the papers (I-squared=0.0%) (**Fig. 2**). Subgroup analysis of low, moderate, and high groups according to the amount of coffee consumption revealed no statistical significance (**Fig. 2**). The P-value of Egger's test for evaluating publication bias was 0.83.

DISCUSSION

Results showed that coffee consumption was not related to AD occurrence. Subgroup analysis also showed similar results. The potential reasons for the conflicting results presented in **Table 1** are as follows.

First, the author evaluated a potential effect based on the difference in research design of the selection criteria among the 4 systematic reviews shown in **Table 1**. To this end, the meta-analysis based only on the 'prospective' cohort studies showed no statistical significance. No statistical significance was detected even after the addition of 2 nested case-control studies[21,22] selected by Barranco Quintana et al.[6] and Liu et al.[7] in **Table 1** (sRR=0.97; 95% CI, 0.12–1.03; I-squared=22.6%).

Second, the author determined a potential effect based on the difference in search strategy in the 4 systematic reviews. The most recently published Larsson and Orsini[9] selected the cohort studies only, so it is reasonable to exclude the 2 nested case-control studies.[21,22] However, given that the search deadline was October 2018, Fischer et al.[23] was included because the

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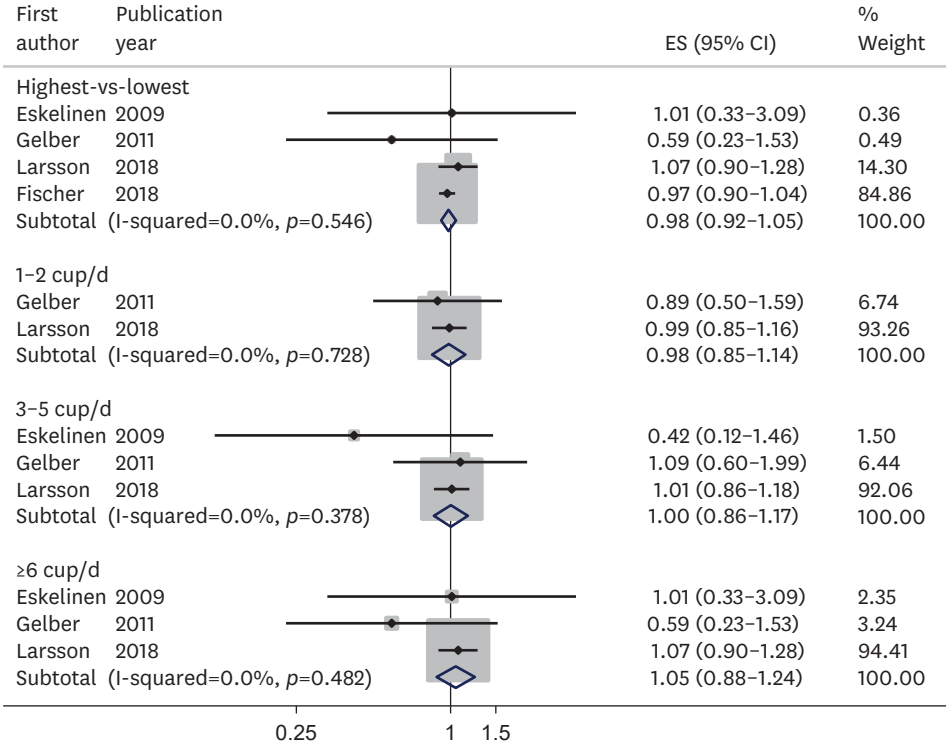

Fig. 2. Forest plot for estimating the summary ES by coffee consumption level.
ES: effect size, CI: confidence interval, cup/d: cup per day.

publication date was June 2018. Meanwhile, Panza et al.[24] indicated that 1 in 4 participants of Lindsay et al.[22] was included in Tyas et al. cohort.[21] Thus, the conclusion of 2 systematic reviews[6,7] selecting 2 nested case-control studies[21,22] may be over-estimated.

Finally, the author determined a potential effect based on the difference in meta-analysis of the extracted information. Wu et al.[8] demonstrated the differences in results with 1–2 cup/d and 3+ cup/d of coffee consumption. Therefore, a subgroup analysis based on the amount of coffee consumption was conducted. No statistical significance was observed between coffee consumption and AD risk.

While considering the 3 potential studies that showed inconsistent results in previous systematic reviews, it is apparent that there was no association between coffee consumption and AD risk. However, it is necessary to consider measurement errors because the level of coffee consumption was measured by a self-reported questionnaire in prospective cohort studies. Further, reverse causality may be involved due to the slow progression of AD during the follow-up.[9] Finally, given recent evidence that AD is triggered by gene-environment interactions,[25] it is necessary to conduct population-based cohort studies involving non-Caucasians.

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