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Midlife Coffee and Tea Drinking and the Risk of Late-Life Dementia: A Population-Based CAIDE Study

Marjo H. Eskelinen[a,*], Tiia Ngandu[a,b], Jaakko Tuomilehto[c,d,e], Hilkka Soininen[a,f] and Miia Kivipelto[a,b,*]
[a]*Department of Neurology, University of Kuopio, P.O. Kuopio, Finland*
[b]*Aging Research Center (ARC), Karolinska Institutet, Stockholm, Sweden*
[c]*Department of Epidemiology and Health Promotion, National Public Health Institute, Helsinki, Finland*
[d]*Department of Public Health, University of Helsinki, Helsinki, Finland*
[e]*South Ostrobothnia Central Hospital, Seinäjoki, Finland*
[f]*Department of Neurology, Kuopio University Hospital, Kuopio, Finland*

Abstract. Caffeine stimulates central nervous system on a short term. However, the long-term impact of caffeine on cognition remains unclear. We aimed to study the association between coffee and/or tea consumption at midlife and dementia/Alzheimer's disease (AD) risk in late-life. Participants of the *Cardiovascular Risk Factors, Aging and Dementia* (CAIDE) study were randomly selected from the survivors of a population-based cohorts previously surveyed within the North Karelia Project and the FINMONICA study in 1972, 1977, 1982 or 1987 (midlife visit). After an average follow-up of 21 years, 1409 individuals (71%) aged 65 to 79 completed the re-examination in 1998. A total of 61 cases were identified as demented (48 with AD). Coffee drinkers at midlife had lower risk of dementia and AD later in life compared with those drinking no or only little coffee adjusted for demographic, lifestyle and vascular factors, apolipoprotein E $\varepsilon 4$ allele and depressive symptoms. The lowest risk (65% decreased) was found in people who drank 3–5 cups per day. Tea drinking was relatively uncommon and was not associated with dementia/AD. Coffee drinking at midlife is associated with a decreased risk of dementia/AD later in life. This finding might open possibilities for prevention of dementia/AD.

Keywords: Alzheimer's disease, coffee, dementia, epidemiology, tea

INTRODUCTION

Coffee and tea are widely consumed around the world. While short-term central nervous system stimulating effects of caffeine are well known [1], the long-term impact remains unclear.

Only three longitudinal studies have investigated the relationship between coffee consumption and dementia/Alzheimer's disease (AD) or cognitive decline. In the Canadian Study of Health and Aging (CSHA) among $\geqslant$65 years old persons, daily coffee drinking decreased the risk of AD by 31% during a 5-year follow-up [2]. Additionally, in the Finland, Italy and the Netherlands Elderly (FINE) Study among elderly men, drinking three cups of coffee per day was associated with the least 10-year cognitive decline [3]. Further, recent results from the Three City Study among $\geqslant$65 years old persons indicated that over three cups of caffeine (from coffee and tea) per day was associated with

*Corresponding authors: Miia Kivipelto, Aging Research Center, NVS, Karolinska Institutet, Gävlegatan 16, 113 30 Stockholm, Sweden. Tel.: +46 73 99 409 22; Fax: +46 8 690 5954; E-mail: Miia.Kivipelto@ki.se. Marjo Eskelinen, Department of Neurology, University of Kuopio, P.O. Box 1627, 70211 Kuopio, Finland. Tel.: +358 40 355 2019; Fax: +358 17 16 2048; E-mail: Marjo.Eskelinen@uku.fi.

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less decline in verbal cognitive functioning and to a lesser extent in visuospatial memory among women but not among men. No relation was found between caffeine consumption and dementia risk over a 4-year period [4]. Tea drinking [5,6], or flavonoid intake from tea [2], on the other hand, has not been associated with a reduced risk of dementia/AD in longitudinal studies.

Findings from cross-sectional studies have been contradictory. Some found no association between coffee drinking and AD [7], while others have indicated an inverse association between caffeine intake (from tea, coffee, and cola drinks) and AD [8]. It has also been shown that coffee consumption improves cognitive performance [9,10], and this may be primarily due to caffeine. Tea drinking has not shown association with dementia/AD in cross-sectional studies [7,11,12], but it has been associated with improved cognitive performance [9]. Also, caffeine has been reported to reduce the risk of Parkinson's disease [13–15]. In principle, case-control studies and studies with short follow-up times are problematic in slowly developing diseases such as AD due to reverse causation.

Very little is known about the possible relations between coffee/tea drinking at midlife and development of dementia later in life. As the pathologic processes leading to dementia start decades before the clinical manifestation of the disease [16], defining risk factors present already at midlife is important. The aim of our study was to investigate the associations of midlife coffee/tea consumption to the development of dementia and AD later in life. Further, we evaluated whether the apolipoprotein E (ApoE) $\varepsilon 4$ allelic status or sex modified the associations.

MATERIALS AND METHODS

Study population

The participants of the *Cardiovascular risk factors, Aging and Dementia* (*CAIDE*) study were randomly selected from survivors of population-based random samples firstly studied within the North Karelia Project and the FINMONICA study in 1972, 1977, 1982 or 1987 (baseline, midlife visit) [17]. A more detailed description of the sampling has been described earlier [17,18]. A random sample of 2000 survivors aged 65–79 years in the end of 1997 and living in the study area in Eastern Finland (in Joensuu or Kuopio) were invited to the re-examination during 1998 (mean (SD) follow-up time 21 (4.9) years) [18]. Altogether 1409 (71%) individuals completed the follow-up examination (late-life visit). These 875 women (62%) and 534 men (38%) had a mean age (SD) of 50.4 (6.0) years at the midlife examination, and 71.3 (4.0) years at the late-life examination. All participants gave a written informed consent in 1998. The study was approved by the local Ethical Committee, and was in accordance with the Helsinki Declaration of 1975.

Measurements

The survey methods used during the baseline (midlife) visit were carefully standardized and complied with international recommendations [19]. In brief, the survey included an exhaustive self-administered questionnaire (on average 135 items) on health behavior (e.g., dietary habits), health status and medical history filled in at home. Systolic (SBP) and diastolic (DBP) blood pressure, height and weight were measured, body mass index (BMI) was calculated, and a venous blood sample was taken to determine serum cholesterol. During the follow-up examination in 1998, the survey methods followed those of the previous surveys in all aspects. Additionally, ApoE genotyping was carried out [20].

Assessment of cognitive status

Cognitive status was assessed using a three-step protocol for the diagnosis of dementia (a screening, a clinical and a differential diagnostic phase). Those individuals scoring $\leqslant$24 on the Mini-Mental State Examination (MMSE) [21] were addressed for further diagnostic examination. The diagnosis of dementia was based on DSM-IV criteria [22] and the probable and possible AD on the NINCDS-ADRDA criteria [23]. A total of 61 persons met the diagnosis of dementia, out of which 48 had AD. The number of demented persons increased to 117 when diagnoses derived from the patient records for the non-participants in the follow-up examination were taken into account.

Dietary assessment

Dietary habits were inquired with a survey questionnaire consisting of approximately 20, mostly qualitative or frequency-based questions, but the consumption of coffee and tea were assessed quantitatively at the midlife examination. Coffee drinking was categorized into three groups: 0–2 cups (low), 3–5 cups (moderate) and $>$5cups (high) per day. Further, the question concerning tea consumption was dichotomized into those not drinking tea (0 cup/day) vs. those drinking tea ($\geqslant$1 cup/day).

Table 1
Characteristics of the participants according to the amount of coffee drunk per day

Coffee drinking, cups/day		0–2 cups/d $n = 223$	3–5 cups/d $n = 641$	>5 cups/d $n = 542$	p-value
Demographic characteristics					
Age at midlife, years		51.1 (6.3)	50.5 (6.2)	49.8 (5.6)	0.02
Age at late-life, years		71.3 (4.1)	71.2 (4.0)	71.3 (4.0)	0.94
Sex: women/men, %		52.5/47.5	70.7/29.3	56.1/43.9	<0.001
Follow-up time, years		20.2 (5.0)	20.7 (5.1)	21.5 (4.6)	0.001
Community, %	Kuopio	45.3	49.0	50.7	0.39
	Joensuu	54.7	51.0	49.3	
Education, years		9.6 (4.0)	8.9 (3.4)	7.9 (3.1)	<0.001
Midlife vascular factors					
Systolic blood pressure, mmHg		146.8 (22.2)	144.2 (19.3)	143.2 (19.4)	0.08
Diastolic blood pressure, mmHg		90.6 (11.6)	89.3 (10.6)	88.5 (11.0)	0.06
Total cholesterol, mmol/l		6.4 (1.2)	6.7 (1.2)	6.9 (1.2)	<0.001
Body mass index, kg/m^2		26.4 (3.8)	26.4 (3.7)	26.8 (3.6)	0.16
Smokers, %		45.3	35.5	50.9	<0.001
Late-life diseases					
Dementia, %		6.7	2.7	5.4	0.01
Alzheimer's disease, %		5.0	2.2	4.3	0.05
Myocardial infarction, %		16.4	12.7	17.0	0.10
Stroke, %		7.9	6.7	7.6	0.79
Diabetes mellitus, %		8.3	5.6	7.3	0.31
Other characteristics					
Beck depression scale in late-life		11.0 (6.9)	9.0 (6.0)	10.0 (7.0)	0.002
ApoE ε4 carriers, %		37.0	36.1	34.2	0.71
Physical activity at midlife, %	Sedentary	56.7	57.3	62.7	0.12
	Active	43.3	42.7	37.3	

Analysis of variance was used for continuous, and χ^2 test for categorical variables. The values are means (standard deviations) unless otherwise stated.

Statistical analyses

All statistical analyses were conducted using SPSS for Windows, version 14.0 (SPSS Inc., Chicago, Illinois). For assessing the differences in characteristics between persons according to their coffee or tea drinking amount, analyses of variance and chi square test (χ^2) tests were run. Logistic regression models were used to analyze independent effect of coffee or tea drinking to the risk of dementia and AD so that the lowest category served as the reference group. Possible confounders were added in blocks in the analyses. Odds ratios (OR) with 95% confidence intervals (CI) were obtained. Model 1 is adjusted for midlife age, sex, education, follow-up time and community of residence. Model 2 is adjusted additionally for midlife smoking, SBP, serum total cholesterol, BMI, and physical activity. Model 3 is adjusted additionally for the ApoE ε4 allelic status, the presence of late-life myocardial infarction (MI)/stroke/diabetes mellitus (DM), and Beck depressive scale. Further, the possible combined effect of ApoE ε4 and coffee/tea drinking, and sex and coffee/tea drinking were investigated first by including interaction terms into the analyses and then by carrying out analyses stratified by ApoE ε4 or sex. The level of significance was $p \leqslant 0.05$ in all analyses.

RESULTS

At midlife, majority of the participants (45.6%) consumed daily moderate (3–5 cups) amounts of coffee, 38.5% consumed high (>5 cups) amounts of coffee, and 15.9% consumed low (0–2 cups) amounts of coffee (Table 1). Majority of the participants (60.5%) did not drink tea, and four fifths of tea drinkers consumed 1–2 cups per day. Persons with low coffee consumption were somewhat older at the midlife examination and more educated compared to those with higher coffee consumption. There were fewer men in the moderate coffee consumption group than in the other two groups. At midlife, the high coffee consumers had the highest serum total cholesterol levels and highest frequency of smoking. At late-life, the low coffee consumers had the highest occurrence of dementia and AD, and the highest scores on the Beck depression scale.

Moderate coffee drinkers had a 65–70% decreased risk of dementia and a 62–64% decreased risk of AD compared with low coffee consumers (Table 2). There was no dose-response between coffee drinking and the risk reduction of dementia and AD. Adjustments for various confounders did not change the results. When we rerun the analyses for dementia including diagnoses

from the patient records for the non-participants in the follow-up, moderate coffee drinkers had a 59–60% decreased risk for dementia compared to the low coffee consumers. Tea consumption (drinking $\geqslant$1 cup of tea/day vs. not drinking) had no associations with dementia/AD (model 2: OR 1.04, 95% CI 0.59–1.84 for dementia, OR 0.91, 95% CI 0.48–1.71 for AD, and OR 1.27, 95% CI 0.84–1.91 for all the demented).

There were no significant multiplicative interactions between the ApoE genotype and coffee/tea drinking for the risk of dementia, but the results concerning coffee drinking were more pronounced among the ApoE ε4 carriers than in non-carriers. In the analyses stratified by the ApoE ε4 carrier status, ORs for dementia among moderate coffee consumers compared to low consumers was 0.32 (0.11-0.92) among the ApoE ε4 carriers and 0.44 (0.12–1.55) among the non-carriers (model 2). For AD, no effect modification by the ApoE ε4 carrier status could be found (results not shown).

There were neither significant multiplicative interactions between the sex and coffee/tea drinking for the risk of dementia and AD, but the results concerning coffee drinking tended to be more pronounced among men. In the analyses stratified by sex, ORs for dementia among moderate coffee consumers compared to low coffee consumers was 0.27 (0.08–0.89) among men and 0.51 (0.17–1.52) among women (model 2). Additionally among men, the risk of dementia was significantly lower also among high coffee consumers compared with low coffee consumers, OR 0.36 (0.13–0.97). For AD, we found no differences between sexes (results not shown).

DISCUSSION

Our findings indicate that moderate coffee consumption at midlife is associated with a decreased risk of dementia and AD in late-life. Tea consumption, however, shows no association with dementia or AD in this study population. The current study is the first to investigate the effects of midlife coffee and tea consumption to the subsequent development of dementia. The results are in accordance with previous report from the CSHA study [2] in the elderly, and now extend the effects to midlife coffee drinking. Given the large amount of coffee consumption globally, the results might have important implications for the prevention or delaying the onset of dementia/AD.

In this study and in the previous longitudinal studies [2,5,6], no association was found between tea drinking and the risk of dementia/AD. This could be due to lesser caffeine content in tea or the fact that other components than caffeine in coffee confer the protective effect. Also, in our study, tea drinking was not very common making statistical power low.

Strengths and limitations

There are several strengths in our study. First, we had a population-based design, high participation rates (80–90% at baseline, 70% at the re-examination), and representation of both women and men, all of which increase the generalizability of our findings. Second, dietary information was collected with the previously validated semi-quantitative food-frequency questionnaire, which is considered as the primary method for dietary assessment in epidemiologic studies because it refers to the whole year and is easy to complete [24]. Third, the information about coffee and tea consumption and other parameters were collected already at midlife (on average 21 years before the diagnosis of dementia), and therefore it was less prone to recall bias or other factors caused by sub-clinical dementia.

Reliance on self-report for data on coffee drinking may constitute a limitation, although we do not believe that this would have lead to systematic errors in reporting coffee drinking habits (i.e., the future dementia did not affect how coffee consumption was reported). Further, we could not make any distinction between filtered, boiled or instant coffee, since we had information about coffee type only from year 1987 (filtered coffee $n = 129$, boiled coffee $n = 63$, instant coffee $n = 6$). Further, we cannot completely exclude the possibility of residual confounding due to measurement error in the assessment of confounding factors, or the potential role of some unmeasured factors. However, we adjusted our analyses for a large number of potential confounding factors, but our results still remained significant. Our sample may have been too small to detect significant differences in the interaction analyses, and to detect possible dose-response effects.

The protective effect of coffee drinking remained unchanged even after adjusting for the two major risk factors for dementia/AD, i.e., hypercholesterolemia and hypertension. Both of them may be influenced by coffee drinking. Previously, it was shown that coffee drinking in the cohorts included in the present study was associated with increased serum cholesterol [25], in particular when boiled, non-filtered coffee was consumed [26]. Since the 1980s, the majority of Finns have changed from boiled coffee to filtered coffee. Al-

Table 2
Association between coffee drinking and dementia

Amount of coffee	Model 1	Model 2	Model 3
Dementia	OR (95% CI)	OR (95% CI)	OR (95% CI)
0–2 cups/d	1 (ref.)	1	1
3–5 cups/d	0.34 (0.16–0.73)	0.35 (0.16–0.75)	0.30 (0.10–0.93)
>5 cups/d	0.61 (0.30–1.21)	0.57 (0.28–1.17)	0.83 (0.32–2.15)
Alzheimer's disease			
0–2 cups/d	1 (ref.)	1	1
3–5 cups/d	0.38 (0.17–0.89)	0.36 (0.15–0.86)	0.42 (0.12–1.46)
>5 cups/d	0.68 (0.31–1.50)	0.61 (0.27–1.37)	1.01 (0.33–3.08)
Dementia (including diagnoses from patient registries for non-participants in follow-up)			
0–2 cups/d	1 (ref.)	1	
3–5 cups/d	0.41 (0.24–0.69)	0.40 (0.24–0.69)	
>5 cups/d	0.61 (0.37–1.02)	0.57 (0.34–0.96)	

Model 1 adjusted for age, sex, education, follow-up time and community of residence.
Model 2 adjusted additionally for midlife smoking, systolic blood pressure, serum total cholesterol, body mass index, and physical activity.
Model 3 adjusted additionally for the ApoE $\varepsilon 4$ carrier status, the presence of late-life myocardial infarction/stroke/diabetes mellitus, and Beck depressive scale.
The participants with missing values for any of the confounders in respective analyses were excluded.

so, the incidence of hypertension was somewhat higher during the follow-up in coffee drinkers compared with non-drinkers [27]. It is therefore interesting to see that coffee seems to reduce the risk of dementia/AD effectively despite these potential negative effects.

Possible mechanisms

It is unknown how coffee would protect from dementia, but there are several hypotheses to explain the association. Coffee drinking has been associated with a decreased risk of type 2 diabetes [28], and one of the proposed mechanisms is that magnesium that is abundant in coffee would increase insulin sensitivity [29]. Diabetes in turn increases the risk of dementia. One pathway could be via insulin degrading enzyme (IDE) that degrades both insulin and amyloid-β [30]. The insulin resistance in type 2 diabetes results in decreased amyloid-β degradation.

Caffeine is a nonselective A_1 and A_{2a} adenosine receptor antagonist, and thereby it stimulates cholinergic neurons [31]. It has been shown in mice that both caffeine and adenosine A_{2a} receptor antagonists prevent amyloid-β induced cognitive deficits [32]. Chronic caffeine administration has shown to have neuroprotective effects in the experimental models of hypoxia and ischemia, also related to caffeine's action as adenosine receptor antagonist [33].

Further, the effect of coffee also may be due to its antioxidant capacity in circulating blood [34]. The most abundant polyphenol in coffee is chlorogenic acid (the ester of caffeic acid with quinic acid) and it is probably responsible for a major part of coffee antioxidants [34]. While vascular risk factors are so important in the development of dementia/AD [35], the role of coffee on vascular risk factors and outcomes is still unclear [36]. Unfiltered coffee increases cholesterol levels, but caffeine might have a positive effect on serum lipids [37].

CONCLUSIONS

From our study, it appears that moderate coffee consumption at midlife may decrease the risk of dementia/AD later in life. The finding needs to be confirmed by other studies, but it opens a possibility that dietary interventions could modify the risk of dementia/AD. Also, identification of mechanisms of how coffee exerts its protection against dementia/AD might help in the development of new therapies for these diseases.

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