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Intakes of caffeine, coffee and tea and risk of Amyotrophic Lateral Sclerosis: Results from five cohort studies

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Abstract

Objective—Caffeine is thought to be neuroprotective by antagonizing the adenosine A_{2A} receptors in the brain and thereby protecting motor neurons from excitotoxicity. We examined the association between consumption of caffeine, coffee and tea and risk of Amyotrophic Lateral Sclerosis (ALS).

Methods—Longitudinal analyses based on over 1 010 000 men and women in 5 large cohort studies [the Nurses' Health Study, the Health Professionals Follow-up Study, the Cancer Prevention Study II Nutrition Cohort, the Multiethnic Cohort Study, and the National Institutes of Health – AARP Diet and Health Study]. Cohort-specific multivariable-adjusted risk ratios (RR) and 95% confidence intervals (CI) estimates of ALS incidence or death was estimated by Cox proportional hazards regression and pooled using random-effects models.

Results—A total of 1279 cases of ALS were documented during a mean of 18 years of follow-up. Caffeine intake was not associated with ALS risk; the pooled multivariable-adjusted RR comparing the highest to the lowest quintile of intake was 0.96 (95% CI 0.81-1.16). Similarly, neither coffee nor tea was associated with ALS risk.

Conclusion—The results of this large study do not support associations of caffeine or caffeinated beverages with ALS risk.

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Keywords

Amyotrophic Lateral Sclerosis; Motor Neuron Disease; caffeine; epidemiology; longitudinal cohort studies

Introduction

Caffeine consumption has been consistently associated with a lower risk of Parkinson Disease (1-6), but its relation to risk of ALS is uncertain. Caffeine is thought to be neuroprotective by antagonizing the adenosine A_{2A} receptors (A_{2A}R) in the brain and thereby protect against excitotoxicity potentially causing neural damage by over-stimulation of glutamate receptors (7) (8).

High coffee intake was associated with lower odds of ALS in a recent case-control study.(9) However, case-control studies are vulnerable to selection and recall bias. We therefore conducted a pooled analysis of five large cohort studies including 1 010 000 men and women and 1279 documented cases of ALS, to examine whether intakes of caffeine, coffee, tea and caffeinated soda are associated with ALS risk.

Methods

Study population

The study population has been described in detail previously (10). In short, the study population comprised the participants in five large cohorts: the Nurses' Health Study (NHS), the Health Professionals Follow-up Study (HPFS), the Cancer Prevention Study II Nutrition Cohort (CPS-II), the Multiethnic Cohort Study (MEC), and the National Institutes of Health – AARP Diet and Health Study (NIH-AARP). All studies have been approved by the institutional review board of the institution where the study was conducted.

Ascertainment of ALS

In all cohorts, vital status and ALS mortality were determined by automated linkage with the National Death Index. The underlying and contributing causes of death were coded according to the International Classification of Diseases (ICD), Ninth Revision. All individuals with ICD-9 code 335.2 (motor neuron disease) or ICD-10 code G.12.2 (motor neuron disease) listed as the underlying or contributing cause of death were considered to have had ALS. In a previous validation study,(11) it was found that ALS was the primary diagnosis listed on death certificates in 89.6% of instances where code 335.2 was listed as a cause or contributory cause of death.(11)

In NHS and HPFS, incident ALS was also documented. In each biennial follow-up questionnaire, participants were asked to report a specific list of medically diagnosed conditions (initially not including ALS) and “any other major illness.” ALS was added to the list of specific conditions on the NHS questionnaires in 1992 onwards and on the HPFS questionnaires in 2000 onwards. We requested permission for release of relevant medical records from participants who reported a diagnosis of ALS on the open question on major

illnesses or on the specific question. Because of the rapidly progressive nature of the disease (median survival 1.5 to 3 years), (12-14) many participants with ALS died before we could send the release request for medical records, so the request was sent to the closest family member. After obtaining permission, we asked the treating neurologists to complete a questionnaire to confirm the diagnosis of ALS and to rate the certainty of the diagnosis (definite, probable, or possible). Starting in 2004 the questionnaire was modified to include the El Escorial criteria. The final confirmation for our study purposes was made by a neurologist with experience in ALS diagnosis based on the review of medical records. We relied on the diagnosis made by the treating neurologist if the information in the medical record was insufficient or if it could not be obtained. Only participants with definite and probable ALS are included as cases in the analyses. When we were unable to confirm (i.e., obtain a copy of the medical record or the neurologist's questionnaire) incident self-reported ALS, we classified the participant as having 'possible ALS' and excluded him or her from the analysis unless death occurred during follow-up and ALS was listed on the death certificate.

Assessment of caffeine, coffee and tea

To assess the average food consumption over the previous year, each cohort used its own validated food frequency questionnaire (FFQ) (15-20). Consumption of coffee and tea were assessed every four years in NHS and HPFS, in 1999 in CPS-IIN, and in baseline questionnaires in MEC and NIH-AARP. Total caffeine intake was calculated at each study site using the U.S. Department of Agriculture food composition sources assuming 137 mg per cup of coffee, 47 mg per cup of tea, 46 mg per can or bottle of cola beverage and 7 mg per serving of chocolate candy. Overall, the largest contributors to caffeine intake were coffee (about 80%) and tea (about 15%). Caffeinated soda contributed about 4% of the total caffeine intake. As coffee and tea have other biologically active principles in addition to caffeine, we evaluated coffee and tea separately in addition to decaffeinated coffee and tea. In NHS, the intake of caffeinated beverages reported on the FFQ, and those estimated from four one-week dietary records were highly correlated; the correlation coefficient was 0.78 for coffee and 0.93 for tea (21). In HPFS, the correlation coefficients were 0.82 for coffee and 0.68 for tea when comparing FFQ intake with two one-week dietary records (22). The correlation coefficients were similar in NIH-AARP; 0.80 for coffee comparing the FFQ with two 24 hour recalls (23). Correlation coefficient for tea has not been reported in NIH-AARP, nor have coefficients for coffee or tea in CPS-IIN or MEC. However, correlation coefficients of other nutrients in these cohorts are comparable to those in NHS, HPFS and NIH-AARP cohorts (24).

Data analysis

All analyses were conducted separately within each cohort. Discrete variables are presented as counts (percentage [%]) and continuous variables as means (standard deviation [SD]). Participants with log-transformed energy intake greater than 3 standard deviations from the study-specific mean were excluded (4%). Person-time was calculated as the date of return of the questionnaire until the date of first onset of ALS symptoms (HPFS, NHS), death from ALS or any other cause, or end of follow-up. The end of follow-up was December 2010 in HPFS, NHS, and CPS-IIN, and December 2011 in MEC and NIH-AARP. For each cohort,

Cox proportional hazards regression was used to estimate relative risks (RR) and 95% confidence intervals (CI) for categories of caffeine, coffee and tea intakes in relation to ALS. Cox models were stratified by age in single years to obtain better age adjustment. We evaluated potential confounders correlated with ALS or coffee intake, and adjusted for smoking (never smoked, pack-years: <10, 10-<20, 20-<30, 30-<40, 40+), education level (<high school, high school, >high school), body mass index (<23, 23-<25, 25-<30, 30), physical activity level (low, medium, high), total energy intake, vitamin E from food and supplements (in quartiles), and dietary carotenoid intake (in quartiles). The association with ALS and smoking (25), vitamin E (26), omega-3 fatty acids (27), and carotenoids (28) in these cohorts have previously been reported. In the main analyses, baseline caffeine, coffee and tea intakes were used in all cohorts. Additional analyses were performed in NHS and HPFS using cumulatively updated exposures. Effect measure modification by smoking (never, past, current), physical activity (, or > cohort specific median), intake of vitamin E (, or > cohort specific median) and carotenoids (, or > cohort specific median) on the association between caffeine intake and ALS was examined by stratification. To minimize the possibility of including participants with ALS symptoms at the time of completing the baseline questionnaire, we excluded the first four years of follow-up in sensitivity analyses. Analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

A total of 494 228 women and 522 775 men (mean age at baseline 59.9 years, SD 8.1) contributed 1279 cases of ALS during a mean follow-up of 18 years and a total of 14 780 144 person-years.

The overall caffeine intake in each cohort ranged from 117.5 mg/day in MEC to 366.4 mg/day in NIH-AARP. Men had a higher overall mean intake of caffeine than women (men: 347 mg/day, women: 250 mg/day, $p<0.0001$) and participants who consumed the most caffeine tended to smoke more and be slightly less physically active than participants with a lower caffeine intake (Table 1). Some overall characteristics are also presented per cohort in eTable1.

A high intake of caffeine was not associated with ALS risk overall; the pooled multivariable-adjusted RR for the highest versus the lowest quintile was 0.96 (95% CI 0.81-1.16, $P_{\text{heterogeneity}}=0.66$) (Table 2). Results were similar among men (RR= 0.96, 95% CI 0.68-1.36, $P_{\text{heterogeneity}}=0.21$) and women (RR = 0.97, 95% CI 0.74-1.29, $P_{\text{heterogeneity}}=0.93$) and across cohorts (eTable 2). For the NHS and HPFS cohorts specifically, results were similar after using cumulatively updated caffeine intake (pooled RR=1.13; 95% CI 0.43-1.84, $P_{\text{heterogeneity}}=0.57$).

Consumption of 4 or more cups of coffee per day, compared to consuming 0 to 3 cups per month, was not associated with ALS risk; pooled multivariable RR was 1.00, 95% CI 0.82-1.22, $P_{\text{heterogeneity}}=0.98$ (Fig 1). Similarly, there was no association between a high tea intake (2 or more cups per day vs 0 to 3 cups per month) and ALS risk (pooled multivariable RR 0.99, 95% CI 0.79-1.23, $P_{\text{heterogeneity}}=0.42$) (Fig 1).

Participants who consumed 2 or more cups of decaffeinated coffee per day had similar ALS risk to non-drinkers (pooled multivariable RR 1.01; 95% CI 0.85-1.19; $I^2=0.48$). Information on decaffeinated tea intake was available only in the CPS-II and NIH-AARP cohorts. In multivariable analyses, use of decaffeinated tea was not associated with ALS risk (pooled RR for 2 or more cups/day vs none = 1.16; 95% CI 0.88-1.52, $I^2=0.45$).

Similarly, consuming 1 or more cans of caffeinated soda per day was not associated with ALS risk (pooled multivariable RR for 1 can/day vs none = 1.02; 95% CI 0.83-1.24, $I^2=0.94$).

Results were similar when we excluded the first 4 years of follow-up to minimize the potential influence of latent diseases on reported caffeine intake at baseline, (pooled multivariable RR 0.98, 95% CI 0.81-1.20). Lastly, we found no indication that the association between caffeine intake and ALS risk was modified by smoking, physical activity or intakes of vitamin E or carotenoids.

Discussion

In these pooled analyses of five large cohorts, neither intake of caffeine, coffee, tea nor caffeinated soda was associated with ALS risk. Results were similar among men and women and in all cohorts.

Our results did not confirm the recently published finding from a case-control study ($n=377$ ALS patients) where a lower ALS risk was reported among ever coffee drinkers drinking >1 cup/day for at least 6 months during lifetime compared with never drinking coffee regularly (9). Reasons for the difference in the findings between our study and the case-control study are unclear, however, it is possible that the results of the case-control study were affected by recall or selection bias.

Although caffeine has neuroprotective effects in animal models of Parkinson's Disease (7), in the only published study in animal models of ALS, caffeine administration was reported to accelerate disease progression and shorten survival in SOD1 mice (29). The results of both epidemiological and experimental studies, therefore, unfortunately suggest that caffeine consumption does not have beneficial effects in the disease process that leads to ALS.

The strengths of our study include a large sample size, validated FFQs and a prospective design, minimizing potential recall bias and misclassifications. The validity of caffeine consumption and coffee intake in our cohorts was assessed directly by comparison with diet records. Further support that our exposure data were assessed reasonably is provided by results from these pooled cohorts that showed inverse association between caffeine and coffee consumption with risk of Parkinson Disease (1, 6, 30) and type 2 diabetes (31, 32), findings that have been independently confirmed in other longitudinal studies and for which there is strong experimental support. Additionally, the ALS cases included in these cohorts are likely to be representative of the whole spectrum of ALS patients, avoiding the selection bias that is often inherent when cases in case control studies are recruited from ALS tertiary-care centers (33, 34). A limitation of our study is the use of ALS mortality as a proxy for ALS incidence in the CPSII, MEC, and NIH-AARP cohorts, which might underestimate

the number of slow-progressing cases, and may have introduced some misclassification of outcome. Nevertheless, bias from this source is likely modest since median survival of ALS patients after diagnosis is relatively short (1.5-3 years) (12), making mortality a reasonable substitute for incidence and death certificates accurately identify 70-90% of cases of ALS or motor neuron diseases (11, 35, 36) although there is some disagreement about the validity of such diagnoses (37).

Generalizability of these results may be limited because of high education levels overall in included cohorts. Further, we acknowledge that a modest association between caffeine intake and ALS cannot be excluded because such association could have been attenuated by measurement error in estimating caffeine intake, which in the MEC, NIH-AARP and CPS-IIN cohorts was assessed at baseline only, and thus does not account for changes in intake during follow-up. On the other hand, the consistency of results in these cohorts with those obtained in NHS and HPFS where caffeine intake was cumulatively updated, suggests that bias from this source is likely to be modest.

In summary, in this large longitudinal study, we found no association between intakes of caffeine, coffee or tea and ALS risk. These results do not support the hypothesis that caffeine intake is associated with a lower risk of ALS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Pooled Relative Risk of Amyotrophic Lateral Sclerosis by Coffee and Tea Intakes in Data from Five Cohort Studies. For coffee, relative risks and 95% confidence intervals were 0.95 (0.82-1.10) for consuming 1 cup of coffee/week to 1 cup/day; 0.99 (0.86-1.14) for consuming 2-3 cups of coffee/day and 1.00 (0.82-1.22) for consuming 4 or more cups of coffee/day compared with consuming 0-3 cups of coffee / month as the referent.

For tea, relative risks and 95% confidence intervals were 0.90 (0.78-1.05) for consuming 1 cup of tea/week to 1 cup/day and 0.99 (0.79-1.23) for consuming 2 cups of tea or more /day compared with consuming 0-3 cups of tea / month as the referent.

Multivariable-adjusted trend across coffee drinkers was $p=0.96$ and across tea drinkers $p=0.79$. P-values for the tests of heterogeneity between studies was $p=0.75$ for coffee and $p=0.52$ for tea. Models were adjusted for age (years), sex, smoking pack years, total calories, body mass index (<23, 23-<25, 25-<30, 30), physical activity (low, average, high), education level (<high school, high school, >high school), dietary and supplementary intake of vitamin E (quartiles) and total carotenoid intake (quartiles).

Table 1

Age-adjusted Characteristics of Study Participants at Baseline According to Caffeine Intake in the Five Cohort Studies.

	Quintile of Caffeine Intake ^a									
	Q1		Q2		Q3		Q4		Q5	
	%	Mean [SD]	%	Mean [SD]	%	Mean [SD]	%	Mean [SD]	%	Mean [SD]
Male gender	42.2		48.1		43.7		50.1		53.7	
Age ^b , years		61.3 [8.7]		60.8 [8.7]		60.9 [8.5]		60.8 [8.5]		59.5 [8.3]
Caffeine, mg/day		13.4 [19.4]		69.1 [54.5]		216.8 [114.0]		413.0 [166.5]		705.5 [345.0]
Coffee, cups/day		0.0 [0.1]		0.2 [0.3]		0.9 [0.7]		2.1 [0.8]		3.6 [1.4]
Tea, cups/day		0.5 [0.9]		0.9 [1.1]		1.0 [1.5]		0.6 [1.0]		0.9 [1.3]
Caffeinated soda ^c , cans/day		0.0 [0.2]		0.2 [0.5]		0.2 [0.7]		0.1 [0.4]		0.3 [0.6]
Decaffeinated coffee ^c , cups/day		0.9 [1.1]		1.4 [1.6]		0.3 [0.9]		0.1 [0.5]		0.1 [0.5]
Decaffeinated tea ^d , cups/day		0.7 [1.1]		0.4 [0.9]		0.1 [0.5]		0.1 [0.5]		0.1 [0.4]
Body mass index		26.2 [5.1]		26.6 [5.0]		26.4 [5.1]		26.3 [4.7]		26.5 [4.9]
Vitamin E intake from diet and supplements, mg/day		78.5 [120.4]		70.8 [112.5]		68.3 [110.7]		66.1 [107.7]		64.0 [107.4]
Total carotenoid intake, mg/day		15.8 [11.3]		14.4 [9.7]		14.3 [9.7]		14.0 [9.2]		13.4 [9.0]
Current smokers	8.1		9.3		11.6		14.7		23.7	
High level of physical activity	28.4		26.8		26.3		26.4		26.1	
Education > high school	74.0		75.3		74.7		76.1		74.9	

Abbreviations: SD = Standard Deviation; HPFS = Health Professionals Follow-up Study; MEC = Multiethnic Cohort Study; CPS-IIN = Cancer Prevention Study II Nutrition Cohort; NIH-AARP = National Institutes of Health – AARP Diet and Health Study; and NHS = Nurses' Health Study.

^a Cohort-specific quintiles

^b Values are not age-adjusted

^c Including NHS, HPFS, CPS-IIN and NIH-AARP cohorts

^d Including CPS-IIN and NIH-AARP cohorts

Table 2
Pooled Relative Risk of Amyotrophic Lateral Sclerosis by Caffeine Intake in Data from Five Cohort Studies.

	Quintile of Caffeine Intake ^a					<i>P</i> _{trend} ^b	<i>P</i> _{heterogeneity} ^c
	Q1	Q2	Q3	Q4	Q5		
No. of cases	268	242	262	261	246		
Age and sex-adjusted RR (95% CI)	1.00 (ref)	0.92 (0.77-1.09)	0.98 (0.83-1.17)	0.98 (0.83-1.17)	0.99 (0.83-1.18)	0.58	0.63
Multivariable-adjusted RR (95% CI) ^d	1.00 (ref)	0.93 (0.78-1.11)	0.98 (0.83-1.17)	0.96 (0.81-1.14)	0.96 (0.81-1.16)	0.83	0.66

Abbreviations: CI = confidence interval; RR =relative risk, ref= reference.

^aCohort-specific quintiles
^b*P* for trend was calculated using median values for each quintile.

^c*P*-values for the tests of heterogeneity between studies were calculated using the Q statistic.

^dAdjusted for age (years), sex, smoking pack years, total calories, body mass index (<23, 23-<25, 25-<30, 30), physical activity (low, average, high), education level (<high school, high school, >high school), dietary and supplementary intake of vitamin E (quartiles) and total carotenoid intake (quartiles).