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Caffeine and alcohol intakes have no association with risk of multiple sclerosis in a prospective study of women

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Abstract

Background—The association between alcohol and caffeine intakes and risk of multiple sclerosis (MS) is unclear; no prospective studies have examined this relationship.

Objective—We examined intakes of alcohol and caffeine in relation to risk of multiple sclerosis.

Design—Intakes of alcohol and caffeine were examined in relation to risk of MS in two large cohorts of women, the Nurses' Health Study (NHS; 92,275 women followed from 1980 to 2004) and Nurses' Health Study II (NHS II; 95,051 women followed from 1991 to 2005). Their diet was assessed at baseline and every 4 years thereafter. During the follow-up, 282 cases of MS were confirmed with onset of symptoms after baseline. 24 cases were missing information on alcohol intake, leaving a total of 258 cases for the alcohol analyses.

Results—Neither total alcohol consumption, not consumption of beer, wine, or liquor was related to MS risk. The multivariable-adjusted pooled RRs comparing categories of alcohol intake to 0 grams/day were 1.07 (95% CI: 0.32–1.99) for 0.1–4.9 grams/day, 1.01 (0.32–1.99) for 5.0–14.9 grams/day, 1.21 (0.69–2.15) for 15.0–29.9 grams/day, and 0.80 (0.32–1.99) for 30+ grams/day; (p for trend 0.89). Caffeine intake was also not significantly associated with MS risk. The multivariable adjusted pooled RR comparing highest to lowest quintile of caffeine intake was 1.14; 95% CI: 0.79–1.66; p for trend 0.71. Consideration of caffeinated and decaffeinated coffee separately also yielded null results.

Conclusion—These results do not support an association between alcohol and caffeine intakes and MS risk.

Alcohol and caffeine are widely consumed substances with prominent effects on the central nervous system.[1] Although numerous longitudinal investigations have been conducted to examine the effects of habitual alcohol and caffeine consumption on several neurological diseases, including stroke[2,3], Alzheimer's[4,5], and Parkinson's[6,7], there are no prospective studies addressing whether alcohol or caffeine consumption affect the risk of developing multiple sclerosis (MS). The relation between alcohol or caffeine consumption and MS risk has only been examined in two case-control studies that generated inconsistent results.[8,9]

In animal experiments, ethanol seems to reduce a subset of CD 8+ T cells that is important for suppressing autoimmune activity, and could thus increase MS risk.[10,11] However, risk of other autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis has been found to be lower in alcohol drinkers as compared to non-drinkers. [12,13] In animal models of MS, chronic caffeine consumption was found to have a neuroprotective effect, potentially through an adenosine A1 receptor-mediated shift from Th1 to Th2 cell

function[14]. However, there is little evidence for an association between caffeine intake and risk of rheumatoid arthritis, a condition that, like MS, is considered to be a cell-mediated autoimmune disease. [15,16]

Here we report the results of the first prospective study assessing the relation between alcohol and caffeine consumption and risk of MS.

Methods

Standard protocol approvals, registrations, and patient consents

This study was approved by the institutional review board of Brigham and Women's Hospital.

Study Population—The Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II) are comprised of female registered nurses living in the United States. The NHS started in 1976 with 121,700 nurses aged 30 to 55; and the NHSII stated in 1989 with 116,671 nurses aged 25 to 42 years. The first dietary assessment was conducted in the NHS in 1980 and in 1991 in NHSII which was considered the beginning of follow up for each cohort. Women were excluded from the analysis if they had implausible caloric intakes (<500 or >3,500 kcal/day in NHS, <800 or >4,200 kcal/day in NHSII) or MS symptoms that started before baseline. After these exclusions, there were 92,275 women in NHS and 95,051 women in NHSII available for the analysis.

Ascertainment of MS cases

Newly diagnosed cases of MS were identified by self report on biennial questionnaires and confirmed by asking the treating neurologist to complete a questionnaire on the certainty of diagnosis (definite, probable, possible, not MS), and clinical history (including date of diagnosis and date of first symptom of MS). In cases where a neurologist did not respond, we mailed a questionnaire to the patient's internist. The treating physician was a neurologist in 90% of women with MS and the diagnosis was supported by positive MRI findings in 76% (NHS) and 89% (NHSII) of the cases; no MRI results were available for the remaining confirmed cases. In this investigation we confirmed cases as those with definite or probable MS according to their neurologist or physician; the validity of this approach has been previously documented.[17] In these analyses, we considered 93 cases of MS (64 definite and 29 probable) in the NHS and 189 cases (136 definite and 53 probable) in the NHSII with onset of symptoms after baseline, for a total of 282 MS cases. 24 cases were missing information on alcohol intake, leaving a total of 258 cases for the alcohol analyses.

Assessment of alcohol and caffeine intake

Comprehensive semi quantitative food frequency questionnaires were completed by participants in the NHS in 1980, 1984, 1986, 1990, 1994, 1998, and 2002 and by those in NHSII in 1991, 1995, 1999, and 2003. The NHS baseline questionnaire contained 61 food items; however, subsequent questionnaires were expanded to approximately 130 items. The validity and reproducibility of these food frequency questionnaires has been previously reported.[18,19] The beverages that contributed to alcohol intake were beer, wine, and liquor. In a validation study, there were high correlations between intakes reported on the FFQ and those estimated from the four 1-week diet records (correlation coefficient for beer 0.94, wine 0.90, liquor 0.84). Similarly, those beverages contributing to caffeine intake also had high correlations (correlation coefficient for coffee 0.78, tea 0.93, cola 0.84).[18]

Statistical analyses

Participants contributed person time to the follow up period from the date of return of their first food frequency questionnaire (1980 in NHS and 1991 in NHS II) to the date of onset of the first symptoms of MS, death from any cause, or end of follow-up (May 31, 2004 for NHS and May 31, 2005 for NHS II). The median time from recruitment in the cohort to MS diagnosis was 7.3 years for NHS and 5.7 years for NHS II. Separate analyses were conducted for each cohort and results were pooled. For main analyses, pre-determined cut points of alcohol intake were used to categorize subjects (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, 30+ grams/day). 15 grams of alcohol is approximately one drink (12oz beer, 4–5oz glass of wine, shot of 80 Proof liquor). Separate effects of beer, wine, and liquor were considered as continuous variables, and reported as relative risks for an increment of 10 grams of alcohol per day. The main analyses for caffeine were conducted by categorizing women into quintiles of intake. Effects of coffee and decaf coffee were also considered in the following categories: never, <1 cup/day, 1–3 cups/day, and >=3 cups/day. To account for changes in consumption over time and to reduce random variation, we used as primary exposures the cumulative averages of alcohol, caffeine or coffee intake calculated from all available dietary questionnaires up to the start of each 2 year follow up period.[20]

Cox proportional hazards models were used to estimate relative risks (RR) adjusted for age (5 year age groups) and other potential risk factors for MS, including intake of total vitamin D from diet and supplements (IUs/day in quintiles), latitude at age 15 (northern, middle, southern states), pack years of smoking (0, <10 pks/yr, 10–24 pks/yr, 25+ pks/yr), and ethnicity (southern European, Scandinavian, other Caucasian, and non-white). Between body mass index during adolescence and alcohol (NHS r2=0.04, N2 r2=0.06) and caffeine intakes correlations were low (NHS r2=0.09, N2 r2=0.08) and therefore not considered in the multivariable adjusted models. Tests for trend were conducted by using the median values of each category of intake as a continuous variable. Pooled RR estimates were calculated by combining data from both cohorts using the inverse of the variance of the relative risk as the weight, and the heterogeneity of the RR estimates from the two cohorts was tested using a Q test, where the squared difference between the log RR was divided by the sum of the variances of each the log RR.[21] All p values were two sided.

Results

Women in the two highest categories of alcohol intake, after adjusting for age, consumed more total calories, had more pack years of smoking, and lower vitamin D intake than non-drinkers (Table 1a). The test for heterogeneity between NHS and NHS II for alcohol was not significant (p=0.78), therefore we pooled the results. Intake of alcohol was not associated with risk of MS (Table 2a). The multivariable-adjusted pooled RRs comparing categories of alcohol intakes versus 0 grams/day of alcohol intake were: 1.07 95% CI: 0.32–1.99 for 0.1–4.9 grams/day; 1.01 95% CI: 0.32–1.99 for 5.0–14.9 grams/day, 1.21 95% CI: 0.69–2.15 for 15.0–29.9 grams/day, and 0.80; 95% CI: 0.32–1.99 for 30+ grams/day; p for trend 0.89). There were no differences between alcohol intake and risk of MS when stratified by age or pack years of smoking (p-values >0.05). Lastly, no associations were found when beer, wine, and liquor were considered separately (Table 3a).

Caffeine intake, similarly to alcohol consumption, was associated with smoking and with lower vitamin D intake. (Table 1b). The test for heterogeneity of the RR estimates relating caffeine consumption to MS risk was not significant (p=0.20), so the results for NHS and NHS II were pooled. No association was found between caffeine intake and risk of MS. The multivariable adjusted pooled RR comparing highest to lowest quintile of caffeine intake was 1.14 (95% CI: 0.79–1.66; p for trend 0.71) (Table 2b). Similar null results were found for caffeinated and decaffeinated coffee (Table 3b).

Discussion

In this large prospective study of women, we found no association between intake of alcohol or caffeine and risk of MS. Specific sources of alcohol and caffeine were also found to have no association with MS risk.

Strengths of our study include its prospective design, a high follow-up response rate, repeated and validated assessments of diet, and detailed data on many potential confounders. These factors reduce the chance that bias influenced our results. Because average alcohol and caffeine intakes were assessed by questionnaires, some misclassification of exposure is inevitable. However, as demonstrated in validation studies among participants in these cohorts, both alcohol and caffeine consumption are reported more accurately than most other dietary items, with correlations between the average intakes reported in the questionnaires and those recorded during four weeks of diet records ranging between 0.78 and 0.93.[18] Further, alcohol intake was further validated by comparison with plasma levels of high-density lipoprotein [22].

An earlier review article of studies of MS cases with and without control groups reported no association between alcohol consumption and risk of MS, but did suggest there may be a link with alcohol abuse [23]. Another population based case control study also found no difference between alcohol consumption of MS patients and the general population [24]. However, significant associations between hard liquor and wine and coffee and tea consumption were reported from two other cases controls studies based in Belgrade and Italy [25,26]. All of these studies which were case control in design, or had no controls, are prone to both recall and selection bias and provide only weak evidence of an association. There may also be confounding by vitamin D intake, which we found to be smaller in the highest categories of alcohol and caffeine intake in our study. MS risk has been documented to be lower in those with the highest intakes of supplemental vitamin D.[27]

In conclusion, the results of this large longitudinal investigation among two well established cohorts of white U.S. women suggest that neither alcohol nor caffeine intake affect the risk of MS.

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Table 1a

Age-Adjusted Baseline Characteristics According to Categories of Alcohol Intakes in NHS and NHS II

	Categories of Alcohol grams/day									
	NHS					NHS II				
	0.0	**0.1–4.9**	**5.0–14.9**	**15.0–29.9**	**30+**	**0.0**	**0.1–4.9**	**5.0–14.9**	**15.0–29.9**	**30+**
N	29,633	30,895	20,598	6,441	4,708	40,587	36,810	14,089	2,541	1,024
Alcohol intake (mean grams/day)	0.0	1.9	9.7	20.9	41.6	0.0	2.1	8.8	20.4	40.8
Beer	0.0	0.23	1.6	3.0	11.3	0.0	0.7	3.7	8.4	19.5
Wine	0.0	1.1	4.2	10.0	9.3	0.0	1.0	3.4	8.2	10.8
Liquor	0.0	0.7	3.9	7.8	20.9	0.0	0.4	1.6	3.9	10.6
Age (y)	46.8	46.8	46.8	46.9	46.9	36.1	36.1	36.2	36.2	36.3
Caffeine intake (mg/day)	361	403	425	428	428	202	259	304	325	358
Vitamin D intake (IU/day)	342	338.	321	305	279	398	391	370	335	308
Total Calories	1564	1536	1551	1626	1764	1769	1779	1835	1927	2008
Pack years smoked	9.0	10.4	13.3	14.9	22.7	6.0	8.2	9.4	10.0	19.8
Latitude at age 15 (%)[†]										
Born in northern tier	26.8	34.3	38.0	38.5	35.3	25.9	32.4	34.2	33.7	30.0
Born in middle tier	42.8	39.9	36.1	35.8	35.1	46.1	43.1	41.0	39.5	43.1
Born in southern tier	7.7	5.4	5.9	6.1	6.2	14.2	11.8	12.6	14.5	15.3
Ethnicity (%)[‡]										
Southern European	12.7	14.6	11.9	10.8	8.9	13.4	14.5	12.7	11.7	11.0
Scandianvian	3.7	3.6	4.5	5.4	4.8	4.3	4.2	4.7	5.6	5.5
Other Caucasian	51	5.3	5.6	5.8	5.5	71.5	73.6	76.3	76.3	77.6
Non-white	2.0	1.8	1.7	1.6	1.7	10.8	7.6	6.3	6.0	6.0

[*] Values are means unless otherwise indicated. All values (except age) are standardized to the age distribution of the study population

[†] Percents may not add up to 100 because of missing values. NHS 0.0: 22.6%, 0.1–4.9: 20.4%, 5.0–14.9: 19.6%, 15.0–29.9: 19.6%, 30+: 23.4%. NHSII 0.0: 13.8%, 0.1–4.9: 12.7%, 5.0–14.9: 12.3%, 15.0–29.9: 12.3%, 30+: 11.6%.

[‡] See above

[†] NHS 0.0: 12.3%, 0.1–4.9: 10.7%, 5.0–14.9: 10.2%, 15.0–29.9: 10.1%, 30+: 13.7%.

Table 1b

Age-Adjusted Baseline Characteristics According to Quintiles of Caffeine Intakes in NHS and NHS II

	Quintiles of Caffeine									
	NHS					NHS II				
	1	2	3	4	5	1	2	3	4	5
N	18,371	18,535	17,905	18,893	18,571	18,788	19,197	18,967	19,078	19,021
Caffeine intake (mg/day)	88.3	245.5	367.0	500.7	749.6	27.5	98.5	184.9	323.5	557.1
Coffee (cups/day)	0.25	1.05	2.11	3.03	4.94	0.02	0.18	0.68	1.84	3.59
Decaf Coffee (cups/day)	0.30	0.49	0.55	0.54	0.49	0.33	0.30	0.35	0.33	0.27
Age (y)	46.7	46.8	46.7	46.6	46.4	35.9	35.8	36.1	36.4	36.7
Alcohol intake (grams/day)	4.4	5.8	7.2	7.3	6.9	1.6	2.2	3.1	4.3	4.4
Vitamin D intake (IU/day)	372	338	325	314	300	440	390	384	381	346
Total Calories	1538	1555	1550	1580	1607	1728	1789	1797	1775	1855
Pack years smoked	7.2	8.3	10.6	12.2	17.7	4.7	5.4	7.1	9.0	11.6
Latitude at age 15(%)[†]										
Northern tier (%)	30.7	33.5	35.6	36.1	33.7	28.7	26.9	29.2	33.4	31.4
Middle tier (%)	43.9	42.1	40.7	38.2	37.7	46.2	46.2	43.3	41.6	42.8
Southern tier (%)	6.7	6.5	6.2	6.6	6.6	12.4	14.1	14.1	12.5	12.2
Ethnicity(%)[‡]										
Southern European	12.8	13.3	13.4	13.3	13.1	12.7	13.5	13.9	14.5	13.9
Scandianvian	4.1	3.7	4.1	4.1	4.6	4.7	4.0	4.2	4.4	4.7
Other Caucasian	5.3	5.5	5.6	5.6	5.4	71.7	73.0	73.0	73.6	74.6
Non-white	20.4	19.9	18.6	17.8	17.5	11.0	9.5	9.0	7.5	6.8

[*] Values are means unless otherwise indicated. All values (except age) are standardized to the age distribution of the study population

[†] Percents may not add up to 100 because of missing values. NHS 0.0: 18.7%, 0.1–4.9: 17.9%, 5.0–14.9: 17.6%, 15.0–29.9: 19.1%, 30+: 22.1%. NHSII 0.0: 12.7%, 0.1–4.9: 12.8%, 5.0–14.9: 13.4%, 15.0–29.9: 12.5%, 30+: 13.7%.

[‡] See above

[†] NHS 0.0: 9.3%, 0.1–4.9: 8.3%, 5.0–14.9: 7.8%, 15.0–29.9: 8.6%, 30+: 10.3%.

Table 2a

Relative Risk of MS in Pooled Analysis for NHS and NHS2 according to category of Alcohol intake

RR and (95% CI) by Category of Alcohol intake						
Alcohol (gm/day)	**0 g/dy**	**0.1–4.9 g/dy**	**5.0–14.9 g/dy**	**15.0–29.9 g/dy**	**30+ g/dy**	**P trend**
Cases/person year	93/1,140,869	99/991,096	47/546,680	14/157,267	5/94,983	
Age Adjusted RR†	1.00	1.15(0.87–1.53)	1.13(0.80–1.61)	1.41(0.80–2.48)	0.97(0.39–2.41)	0.56
Multivariable RR§	1.00	1.07(0.81–1.43)	1.01(0.71–1.44)	1.21(0.69–2.15)	0.80(0.32–1.99)	0.89

†Relative Risk and 95% confidence interval from age (5 year categories) adjusted cox proportional hazards model

§Relative Risk and 95% confidence interval from model above (†) additionally controlling for intake of vitamin D (IUs/day in quintiles), latitude at age 15 (northern, middle, southern states), pack years of smoking (0, <10 pks/yr, 10–24 pks/yr, 25+ pks/yr), and ethnicity (southern European, Scandinavian, other Caucasin, and non-white)

₪Calculated using medians of alcohol categories

Table 2b

Relative Risk of MS in Pooled Analysis for NHS and NHS2 according to intake of caffeine

RR and (95% CI) by Quintile of Caffeine						
Caffeine (mg/day)	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**P trend**
Cases/person year	53/678,769	55/685,871	51/682,902	50/614,816	73/675,349	
Age Adjusted RR†	1.00	1.03(0.70–1.50)	0.97(0.66–1.43)	0.95(0.64–1.40)	1.39(0.97–1.98)	0.12
Multivariable RR§	1.00	0.99(0.68–1.44)	0.90(0.61–1.32)	0.83(0.56–1.22)	1.14(0.79–1.66)	0.71

†Relative Risk and 95% confidence interval from age (5 year categories) adjusted cox proportional hazards model

§Relative Risk and 95% confidence interval from model above (†) additionally controlling for intake of vitamin D (IUs/day in quintiles), latitude at age 15 (northern, middle, southern states), pack years of smoking (0, <10 pks/yr, 10–24 pks/yr, 25+ pks/yr), and ethnicity (southern European, Scandinavian, other Caucasin, and non-white)

₪Calculated using medians of quintiles of caffeine

Table 3a

Relative Risk of MS in Pooled Analysis by Type of Alcohol in NHS and NHS2

	RR and (95% CI)
Beer (10 gm/day)	
Age Adjusted RR†	0.99(0.72–1.38)
Multivariable RR§	0.93(0.66–1.3)
Liquor (10 gm/day)	
Age Adjusted RR†	1.13(0.94–1.37)
Multivariable RR§	1.01(0.76–1.34)
Wine (10 gm/day)	
Age Adjusted RR†	1.06(0.81–1.39)
Multivariable RR§	1.10(0.91–1.33)

† Relative Risk and 95% confidence interval from age (5 year categories) adjusted cox proportional hazards model

§ Relative Risk and 95% confidence interval from model above (†) additionally controlling for intake of vitamin D (IUs/day in quintiles), latitude at age 15 (northern, middle, southern states), pack years of smoking (0, <10 pks/yr, 10–24 pks/yr, 25+ pks/yr), and ethnicity (southern European, Scandinavian, other Caucasin, and non-white)

Table 3b

Relative Risk of MS by type of coffee in pooled NHS and NHS2

RR and (95% CI)					
Coffee (cups/day)	**Never**	**<1 cup/dy**	**1–3 cups/dy**	**>=3 cups/dy**	**P trend**
Cases/person year	79/379,258	47/347,727	112/731,939	44/264,069	
Age Adjusted RR†	1.00	0.90(0.62–1.29)	1.05(0.78–1.40)	1.21(0.83–1.76)	0.20
Multivariable RR§	1.00	0.87(0.60–1.26)	0.93(0.69–1.26)	0.98(0.66–1.44)	0.95
Decaf (cups/day)	Never	<1 cup/dy	1–2 cups/dy	>=2 cups/dy	
Cases/person year	167/887,998	91/587,723	12/150,989	12/96,283	
Age Adjusted RR†	1.00	1.02(0.63–1.66)	0.76(0.32–1.79)	1.27(0.64–2.50)	0.97
Multivariable RR§	1.00	0.97(0.59–1.59)	0.71(0.30–1.68)	1.16(0.58–2.29)	0.73

†Relative Risk and 95% confidence interval from age (5 year categories) adjusted cox proportional hazards model

§Relative Risk and 95% confidence interval from model above (†) additionally controlling for intake of vitamin D (IUs/day in quintiles), latitude at age 15 (northern, middle, southern states), pack years of smoking (0, <10 pks/yr, 10–24 pks/yr, 25+ pks/yr), and ethnicity (southern European, Scandinavian, other Caucasin, and non-white)

₪Calculated using medians of coffee categories