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Coffee, Tea, and Caffeine Intake and Amyotrophic Lateral Sclerosis Mortality in a Pooled Analysis of Eight Prospective Cohort Studies

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ABSTRACT

Background: Caffeine is associated with a lower risk of some neurological diseases, but few prospective studies have investigated caffeine intake and risk of amyotrophic lateral sclerosis (ALS) mortality. We therefore determined associations between coffee, tea, and caffeine intake and risk of ALS mortality.

Methods: We conducted pooled analyses of eight international, prospective cohort studies, including 351,565 individuals (120,688 men and 230,877 women). We assessed coffee, tea, and

caffeine intake using validated food frequency questionnaires administered at baseline. We used Cox regression to estimate study- and sex-specific risk ratios (RR) and 95% confidence intervals (CI) for ALS mortality, which were then pooled using a random effects model. We conducted analyses using cohort-specific tertiles, absolute common cut points, and continuous measures of all exposures.

Results: During follow-up, 545 ALS deaths were documented. We did not observe statistically significant associations between coffee, tea, or caffeine intake and risk of ALS mortality. The pooled multivariable RR (MVRR) for ≥3 cups per day vs. >0 to <1 cup per day was 1.04 (95% CI: 0.74–1.47) for coffee and 1.17 (95% CI: 0.77–1.79) for tea. The pooled MVRR comparing the highest to the lowest tertile of caffeine intake (mg/day) was 0.99 (95% CI: 0.80–1.23). No statistically significant results were observed when exposures were modeled as tertiles or continuously.

Conclusions: Our results do not support associations between coffee, tea, or total caffeine intake and risk of ALS mortality.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a rare neurologic disease, characterized by motor neuron degeneration and loss of voluntary movement, with few effective treatments and poorly understood etiology [1]. The role of caffeine in ALS risk is of interest given its inverse associations with Parkinson's disease [2] and dementia [3]. It has been suggested that caffeine may be neuroprotective through inhibition of adenosine A2a receptors, which may modulate dopaminergic transmission [4] and mitigate neurotoxicity [5]. However, the two epidemiologic studies that have examined associations between coffee, tea, and caffeine intake and ALS risk have yielded conflicting results. A retrospective case-control study suggested a possible preventive role of coffee consumption [6], but a more recent pooled analysis of five U.S.-based prospective cohort studies found no association between coffee, tea, soda, or caffeine intake and ALS risk [7]. These inconsistencies led us to conduct an international, pooled analysis of eight prospective cohort studies to assess whether coffee, tea, and caffeine intake are associated with risk of ALS mortality.

METHODS

Study Population. This study was conducted in eight prospective cohort studies within the Pooling Project of Prospective Studies of Diet and Cancer (DCPP) [8-16] that met predefined criteria for inclusion in the consortium [16, 17], identified at least 15 deaths due to ALS (ICD-9 code 335.2 or ICD-10 code G12.2), and were not in a prior consortial project of ALS by our group [7] (**Table 1**). All studies were reviewed and approved by the institutional review board of the institution at which the study was conducted, and all participants gave informed consent for their participation.

Exposure Assessment. Each study assessed baseline consumption of foods and beverages over the past year using a validated food frequency questionnaire (FFQ) [18-25]. Based on available data in each study, we performed our analyses using two major beverage groups: total coffee (summing grams per day of regular, decaffeinated, and/or unidentified type of coffee) and total tea (summing grams per day of caffeinated, caffeine-free, herbal tea, and/or unidentified type of tea). Each cohort except WLHS derived a total caffeine variable using all relevant beverages and foods in their FFQ by multiplying the frequency of consumption of each item, the portion size listed, and the caffeine content of the portion reported.

Although all studies conducted validation studies of their questionnaires, not all studies validated coffee, tea, and caffeine intake specifically. However, the studies that did report these estimates showed correlation coefficients for coffee, tea, and caffeine intake ranging between 0.5 and 0.9 when comparing intake from FFQs against intake via multiple dietary records or 24-hour recalls [18-20, 26-28].

Assessment of Non-dietary Covariates. Non-dietary information, including age, body weight, height, race, education attained, and smoking history, was collected in each cohort at baseline using self-administered questionnaires, and all data were harmonized across studies.

Statistical Analysis. In addition to study-specific exclusion criteria, we excluded participants whose energy intakes were outside 3 standard deviations from the study-specific $\log_e$-transformed mean energy intake to remove individuals who likely filled out their FFQ incorrectly. Participants contributed person-years of follow-up time from the date of the baseline questionnaire to the date of death, loss to follow-up, if available, or administrative end of follow-up, whichever came first.

All analyses were conducted using the Statistical Analysis System (SAS) software version 9.3 (Cary, NC). Intakes of coffee, tea, and caffeine were categorized by study-specific tertiles and by common absolute cut-points (g/day approximating cups/day for coffee and tea, mg/day for caffeine). We used a two-stage method to estimate pooled risk ratios (RR). First, we estimated study- and sex-specific RRs and 95% confidence intervals (CI) between each exposure and risk of ALS mortality, using Cox regression [16]. We adjusted for age, calendar time, and time since entry into the study by stratifying by age at baseline (years) and year of questionnaire return. We ran additional models adjusting for total energy intake, race, education, body mass index (BMI), and smoking habits, and further mutually adjusted for coffee and tea (see footnote 1 in Table 2). In the second stage, we combined study-specific $\log_e$ RRs, weighted by the inverse of their variance, using a random effects model [16].

We assessed whether each association was consistent with linearity by examining nonparametric regression curves using restricted cubic splines [16, 17]. These analyses combined all studies into a single dataset (i.e., one-stage, aggregated approach), stratified by age, the year that the questionnaire was returned, and study, and included the other covariates in the model.

We tested for potential effect modification by BMI ($<25 kg/m^2$ vs. $\geq 25 kg/m^2$) and smoking status (ever- vs. never-smokers at baseline) using a mixed effects meta-regression model [16], and evaluated the statistical significance of the parameter estimate using the Wald test. Lastly, we conducted sensitivity analyses excluding individuals who died from ALS within the first two years of follow-up, since undiagnosed symptoms of ALS may affect caffeinated beverage

consumption, and further reanalyzed all associations using a one-stage approach for pooling rather than the two-stage approach.

RESULTS

In the pooled cohort of 351,565 participants, followed for a maximum of 12 to 24 years, we identified 545 ALS deaths (**Table 1**). Median coffee and tea intake varied at least 4-fold across studies, and median caffeine intake varied almost 3-fold across studies.

Because age- and multivariable-adjusted results were similar, we only report associations using multivariable models. We observed pooled multivariable RRs (MVRR) comparing the highest to the lowest tertile of intake of 1.02 (95% CI: 0.81–1.27) for coffee intake, 0.97 (95% CI: 0.78–1.19) for tea intake, and 0.99 (95% CI: 0.80–1.23) for caffeine intake (**Table 2)**. We similarly observed no statistically significant associations when exposures were modeled using absolute common cut-points (**Table 3**). The pooled MVRR for individuals who drank on average 3 or more 8oz cups of coffee per day compared to those who drank between 0.1 and 1 8oz cup of coffee per day on average was 1.04 (95% CI: 0.74–1.47). The pooled MVRR for those who drank on average 3 or more 8oz cups of tea per day compared to those who drank >0 to <1 8oz cup of tea per day on average was 1.17 (95% CI: 0.77–1.79). For both coffee and tea, nondrinkers did not have a statistically significant difference in risk of ALS mortality compared to those who drank >0 to <1 8oz cup of the respective beverage per day. The pooled MVRR for those who consumed on average 500mg/day or more of caffeine compared to 50- <250mg/day was 1.10 (95% CI: 0.84–1.44). Those who consumed less than 50mg/day of caffeine also did not have a statistically significant difference in risk of ALS mortality compared to the same reference group. There was no evidence of heterogeneity by study (P≥0.10) or sex (P>0.25) for all analyses.

There was no evidence of nonlinearity for any of the associations ($P_{nonlinearity}$ >0.10 for all associations), so we conducted analyses in which each exposure was modeled continuously. We did not observe any statistically significant associations for any of these analyses (**Supplementary Table 1, Figure 1)**.

There was evidence of marginally statistically significant effect modification by smoking for tea intake and risk of ALS mortality ($P_{interaction}$=0.07). However, associations were statistically non-significant in both ever-smokers (HR=0.96, 95% CI: 0.87–1.06) and never-smokers (HR=1.05, 95% CI: 0.94–1.17). We did not find any evidence of effect modification by smoking for associations with coffee or caffeine intake, or by BMI for associations with any exposure ($P_{interaction}$>0.12, results not shown).

Results for all analyses were similar when we used a one-stage method for pooling the data. The one-stage method allowed us to compare the highest category to the lowest category for each exposure when analyzing categories of intake defined by absolute common cut-points. The pooled MVRRs were 1.07 (95% CI: 0.79–1.45) for those who drank on average 3 or more cups of coffee per day compared to those who did not drink coffee, 0.96 (0.66–1.42) for those who drank on average 3 or more cups of tea per day compared to those who did not drink tea, and 1.11 (95% CI: 0.86–1.45) for those who consumed on average 500mg/day or more compared to 0mg/day of caffeine. When we excluded the 25 cases diagnosed in the first two years of follow-up, we observed similar results to those from the primary analyses.

DISCUSSION

In this pooled analysis of eight prospective cohort studies including 545 ALS deaths, we found no statistically significant associations between habitual coffee, tea, or caffeine intake and risk of ALS mortality. These findings are consistent with a pooled analysis of five different cohorts, which also did not observe statistically significant associations for coffee, tea, or caffeine intake [7]. While a case-control study suggested an inverse association between coffee intake and ALS risk, its retrospective nature makes it vulnerable to recall and selection bias [6]. Moreover, this study had not hypothesized an inverse association for coffee *a priori*, so this finding may have been due to chance.

A major strength of this study includes its large size and inclusion of many studies, which allowed for prospective examination of a rare outcome across different populations and

geographic regions. Indeed, because ALS deaths are rare within individual cohorts, aggregation of multiple cohorts is the most feasible way to improve statistical power and report on such associations. Additionally, all studies validated their dietary assessment instrument, and correlation coefficients between FFQ and dietary record intakes for tea, coffee, and caffeine were high in studies that had published these measures of validity. Lastly, because we had primary data from all studies, we harmonized all exposures, outcomes, and adjusted covariates, which may reduce heterogeneity between these studies.

This study also has several limitations. We had limited power to detect modest associations between caffeinated beverage intake and risk of ALS mortality given the number of ALS deaths that occurred in these eight cohorts. Moreover, because we only had data on intake at baseline, we could not examine duration or history of caffeine exposure, and could not assess changes in diet over time, which may be important given that caffeine intake has been observed to change over discrete age groups, with highest intake among middle-aged adults, and lower intake among younger adults and the elderly [29]. At the same time, regular consumption of coffee and tea is less prone to within-person variation in intake, which reduces measurement error [30]. The included studies varied in dietary evaluation, data collection, and assessment of confounding variables, and so there may be undetected heterogeneity between studies. However, we harmonized the exposure, confounding variables, and outcome data to reduce this heterogeneity. Lastly, because we only had data on ALS mortality, as opposed to ALS onset, we may have underestimated the number of true ALS cases, especially slow-progressing cases, for whom our results may not be generalizable. Previous research suggests that up to 30% of cases may be unreported using mortality data [31]. However, the median survival after ALS diagnosis is approximately 1.5 to 4 years [32], and the studies included in our analysis had at least 12 years of follow-up, decreasing the possibility of missing most slow-progressing cases. Moreover, it is unlikely that any misclassification would vary across coffee, tea or caffeine intake because all exposures were measured prospectively, and factors associated with coffee, tea, or caffeine intake that might affect the accuracy of death certificates (e.g. age, smoking, BMI, and education) were included in the models.

In summary, this pooled analysis of eight prospective cohort studies does not support any associations between coffee, tea, or caffeine intake and risk of ALS mortality, despite observed inverse associations between caffeine and other neurological diseases [2, 3]. Future studies examining associations between caffeine intake and ALS phenotype or progression may be warranted given the suggested neuroprotective role of caffeine in these other diseases.

DISCLOSURE OF CONFLICT OF INTEREST

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FIGURE 1 LEGEND

The black squares and horizontal lines correspond to the study-specific risk ratios and 95% confidence intervals, respectively. The area of the black squares is proportional to the inverse of the sum of between-studies variance and study-specific variance. The diamond represents the pooled multivariable risk ratio and 95% confidence interval. All models were adjusted for race (Caucasian, African-American, Asian, Hispanic, other), energy intake (continuous), education (<high school, high school, >high school), body mass index (<23, 23-<25, 25-<30, ≥30 kg/m^2), and smoking habits (never, >0-<10, 10-<20, 20-<30, 30-<40, ≥40 pack-years). Age in years and year of questionnaire return were included as stratification variables.

Table 1. Characteristics of the Studies included in the Pooled Analysis of Coffee, Tea, and Caffeine Consumption and Risk of Amyotrophic Lateral Sclerosis Mortality[a]

Sex	Study[b]	Country	Follow-up	Baseline cohort size	Total cases	Age range (years)	% Ever-Smokers	Median BMI (kg/m^2)	Coffee intake (g/day)[c]	Tea intake (g/day)[c]	Caffeine intake (mg/day)[c,d]
Male	COSM	Sweden	1998-2010	45,338	74	45-79	64	25.2	636 (169 - 1272)	0 (0 - 543)	444 (190 - 848)
	MCCS	Australia	1990-2006	14,824	28	27-75	57	26.8	500 (0 - 900)	200 (0 - 900)	442 (84 - 834)
	NLCS	Netherlands	1986-2003	30,363	83	55-69	88	24.9	500 (250 - 875)	250 (0 - 625)	386 (203 - 629)
	PLCO	USA	1993-2009	30,163	32	55-74	63	27.0	875 (2 - 2248)	22 (0 - 548)	381 (26 - 1159)
Female	IWHS	USA	1986-2009	34,588	91	55-69	34	25.2	597 (0 - 1311)	19 (0 - 237)	150 (7 - 639)
	MCCS	Australia	1990-2006	22,830	36	27-76	31	25.7	190 (0 - 855)	400 (0 - 1000)	342 (79 - 783)
	NLCS	Netherlands	1986-2003	22,550	63	55-69	42	24.7	500 (250 - 750)	375 (0 - 750)	370 (186 - 543)
	PLCO	USA	1993-2009	28,315	27	55-74	43	25.9	842 (0 - 2105)	47 (0 - 822)	337 (13 - 951)
	SMC	Sweden	1986-2010	36,630	51	40-76	46	24.5	492 (164 - 855)	32 (0 - 444)	347 (167 - 625)
	WHS	USA	1986-2009	38,387	42	45-89	49	25.0	592 (0 - 1107)	33 (0 - 592)	284 (21 - 645)
	WLHS	Sweden	1986-2007	47,577	18	30-49	59	22.9	443 (63 - 885)	49 (0 - 295)	--
Total				351,565	545						

[a]Definition of caffeinated beverage variables: coffee intake included regular coffee, decaffeinated coffee, and coffee with unknown caffeine content; tea intake included caffeinated, caffeine-free, and herbal teas; caffeine intake was estimated by individual studies

[b]COSM, Cohort of Swedish Men; MCCS, Melbourne Collaborative Cohort Study; NLCS, Netherlands Cohort Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; IWHS, Iowa Women's Health Study; SMC, Swedish Mammography Cohort; WHS, Women's Health Study; WLHS, Women's Lifestyle and Health Study

[c]Median intake (10th percentile - 90th percentile)

[d]Caffeine intake could not be calculated for WLHS because of lack of available data

Table 2. Pooled Multivariable Relative Risks (MVRR)[a] and 95% Confidence Intervals (95% CI) for Tertiles of Coffee, Tea, and Caffeine Intake and Risk of Amyotrophic Lateral Sclerosis Mortality

	Study-Specific Tertiles of Intake			P for trend	P for heterogeneity	
	1	2	3		By study[b]	By sex[c]
Coffee intake (g/day)[d]						
Men						
No. of cases	107	53	57			
MVRR (95% CI)	1.00 (ref)	0.87 (0.60-1.24)	1.09 (0.76-1.58)	0.81	0.38	
Women						
No. of cases	127	103	98			
MVRR (95% CI)	1.00 (ref)	0.90 (0.69-1.18)	0.97 (0.73-1.29)	0.71	0.84	
Combined						
No. of cases	234	156	155			
MVRR (95% CI)	1.00 (ref)	0.89 (0.72-1.09)	1.02 (0.81-1.27)	0.59	0.81	0.61
Tea intake (g/day)[e]						
Men						
No. of cases	115	43	59			
MVRR (95% CI)	1.00 (ref)	1.01 (0.69-1.47)	0.84 (0.59-1.18)	0.69	0.38	
Women						
No. of cases	138	83	107			
MVRR (95% CI)	1.00 (ref)	0.85 (0.64-1.14)	1.06 (0.81-1.39)	0.51	0.50	

Combined						
No. of cases	253	126	166			
MVRR (95% CI)	1.00 (ref)	0.91 (0.72-1.14)	0.97 (0.78-1.19)	0.45	0.47	0.28
Caffeine intake (mg/day)						
Men						
No. of cases	89	50	76			
MVRR (95% CI)	1.00 (ref)	0.66 (0.47-0.94)	1.06 (0.76-1.48)	0.74	0.74	
Women[f]						
No. of cases	101	116	93			
MVRR (95% CI)	1.00 (ref)	1.14 (0.86-1.49)	0.94 (0.70-1.26)	0.40	0.85	
Combined[f]						
No. of cases	190	166	169			
MVRR (95% CI)	1.00 (ref)	0.90 (0.69-1.17)	0.99 (0.80-1.23)	0.69	0.94	0.60

[a]All models adjusted for race (Caucasian [ref], African-American, Asian, Hispanic, other), calories (continuous), education (<high school [ref], high school, >high school), body mass index (BMI, kg/m^2) (<23 [ref], 23-<25, 25-<30, ≥30), smoking (never [ref], >0-<10, 10-<20, 20-<30, 30-<40, ≥40 pack-years). Age in years and year of questionnaire return were included as stratification variables.

[b]Test for between-studies heterogeneity in the highest tertile (calculated using Q statistic)

[c]Test for between-studies heterogeneity due to sex in the highest tertile (calculated using Wald statistic)

[d]Additionally adjusted for tea intake (0 [ref], >0-1, >1-3, >3 cups/day)

[e]Additionally adjusted for coffee intake (0 [ref], >0-1, >1-3, >3 cups/day)

[f]Excludes Women's Lifestyle and Health Study (WLHS) because this study did not derive a total

caffeine variable

Table 3. Pooled Multivariable Relative Risks (MVRR)[a] and 95% Confidence Intervals (95% CI) for Categories of Coffee, Tea, and Caffeine Intake and Risk of Amyotrophic Lateral Sclerosis Mortality

						P for heterogeneity	
	Categories (per day)[b]				P for trend	By study[c]	By sex[d]
Coffee intake (cups/day)[e]	0	>0-<1 cup	1-<3 cups	≥3 cups			
Men							
No. of cases	20	28	92	77			
MVRR (95% CI)	1.43 (0.78-2.60)	1.00 (ref)	0.92 (0.56-1.52)	0.94 (0.56-1.55)	0.63	0.71	
Women[f]							
No. of cases	31	48	159	90			
MVRR (95% CI)	1.09 (0.59-2.03)	1.00 (ref)	0.99 (0.60-1.63)	1.06 (0.62-1.82)	0.71	0.12	
Combined[f]							
No. of cases	51	76	251	167			
MVRR (95% CI)	1.27 (0.86-1.87)	1.00 (ref)	0.98 (0.71-1.37)	1.04 (0.74-1.47)	0.99	0.29	0.64
Tea intake (cups/day)[g]	0	>0-<1 cup	1-<3 cups	≥3 cups			
Men							
No. of cases	63	50	85	19			
MVRR (95% CI)	0.95 (0.62-1.45)	1.00 (ref)	0.99 (0.67-1.47)	1.15 (0.54-2.42)	0.29	0.17	
Women[h]							
No. of cases	109	113	87	19			
MVRR (95% CI)	1.36 (0.90-2.05)	1.00 (ref)	1.58 (1.10-2.27)	1.12 (0.60-2.10)	0.91	0.68	
Combined[h]							

No. of cases	172	163	172	38			
MVRR (95% CI)	1.15 (0.88-1.51)	1.00 (ref)	1.29 (0.96-1.71)	1.17 (0.77-1.79)	0.48	0.50	0.85
Caffeine intake (mg/day)	<50mg	50-<250mg	250-<500mg	≥500 mg			
Men							
No. of cases	16	39	84	76			
MVRR (95% CI)	1.92 (1.03-3.57)	1.00 (ref)	0.91 (0.60-1.36)	1.24 (0.82-1.88)	0.84	0.48	
Women[i]							
No. of cases	44	78	131	57			
MVRR (95% CI)	1.16 (0.69-1.93)	1.00 (ref)	1.15 (0.85-1.55)	1.01 (0.70-1.44)	0.79	0.70	
Combined[i]							
No. of cases	60	117	215	133			
MVRR (95% CI)	1.29 (0.90-1.85)	1.00 (ref)	1.06 (0.83-1.35)	1.10 (0.84-1.44)	0.95	0.73	0.45

[a]All models adjusted for race (Caucasian [ref], African-American, Asian, Hispanic, other), calories (continuous), education (<high school [ref], high school, >high school), body mass index (BMI, kg/m^2) (<23 [ref], 23-<25, 25-<30, ≥30), smoking (never [ref], >0-<10, 10-<20, 20-<30, 30-<40, ≥40 pack-years). Age in years and year of questionnaire return were included as stratification variables.

[b]One cup is equivalent to 8 ounces (237 grams)

[c]Test for between-studies heterogeneity in the highest category (calculated using Q statistic)

[d]Test for between-studies heterogeneity due to sex in the highest category (calculated using Wald statistic)

[e]Additionally adjusted for tea intake (0 [ref], >0-<1, 1-<3, ≥3 cups/day)

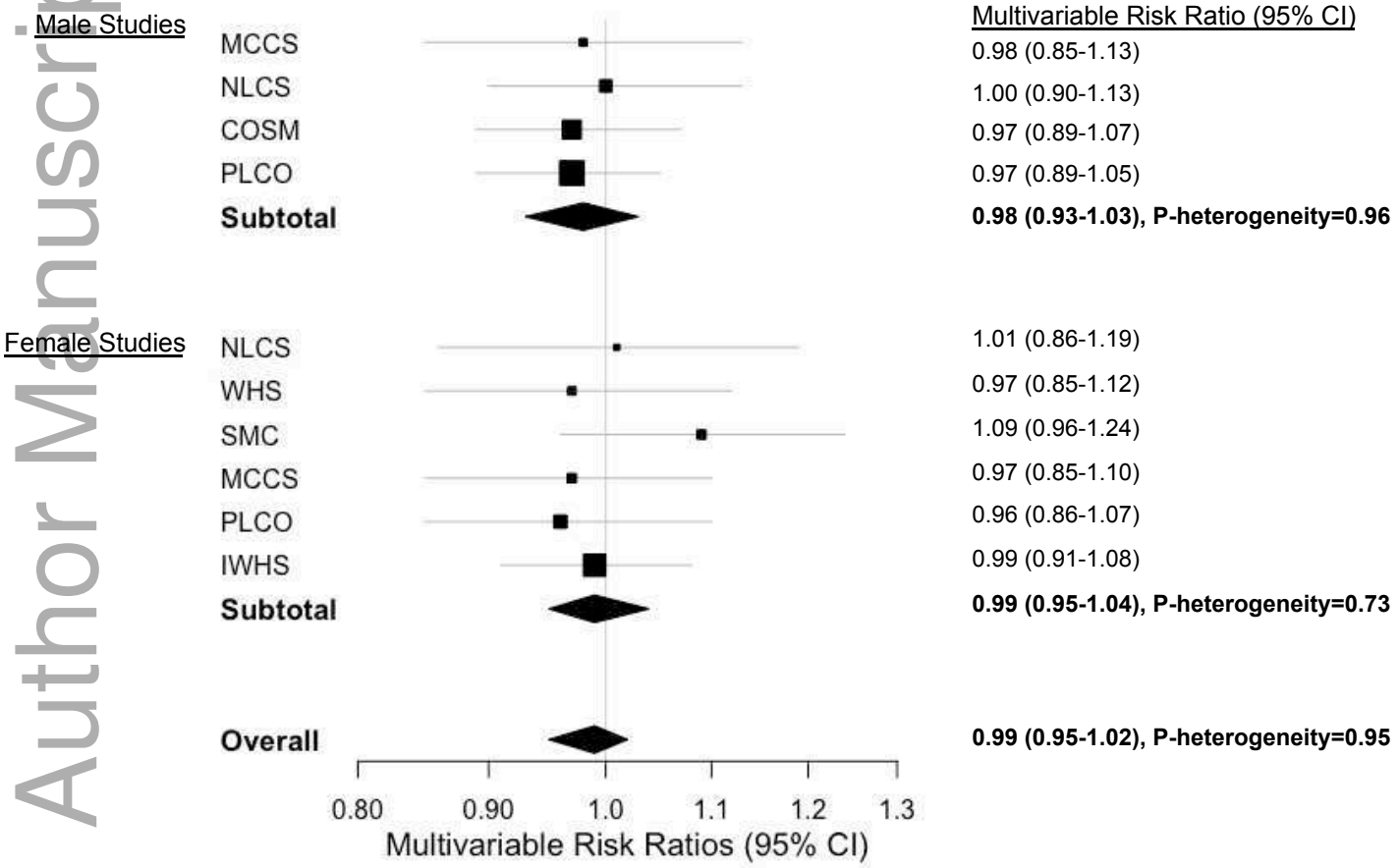
[f]Swedish Mammography Cohort (SMC) and Women's Lifestyle Validation Study (WLHS) were excluded from the first category (0 cups/day) because there were no cases in this category for these studies. The participants in this study who were in these categories and were not cases were included in the next highest category.

[g]Additionally adjusted for coffee intake (0 [ref], >0-<1, 1-<3, ≥3 cups/day)

[h]SMC and WLHS were excluded from the last category (≥3 cups/day) because there were no cases in this category for these studies. The participants in this study who were in these categories and were not cases were included in the next highest category.

[i]WLHS was excluded from these analyses because this study did not derive a total caffeine intake variable. SMC was excluded from the first category (<50 mg/day) because there were no cases in this category for this study. The participants in this study who were in these categories and were not cases were included in the next highest category.

Figure 1. Multivariable Risk Ratios and 95% Confidence Intervals (CI) for Risk of Amyotrophic Lateral Sclerosis Mortality and Caffeine Intake (per 100mg/day increase) by Study, Sex, and Overall



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