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Caffeinated Coffee and Tea Consumption, Genetic Variation and Cognitive Function in the UK Biobank

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ABSTRACT

Background: Coffee and tea are the major contributors of caffeine in the diet. Evidence points to the premise that caffeine may benefit cognition.

Objective: We examined the associations of habitual regular coffee or tea and caffeine intake with cognitive function whilst additionally accounting for genetic variation in caffeine metabolism.

Methods: We included white participants aged 37–73 y from the UK Biobank who provided biological samples and completed touchscreen questionnaires regarding sociodemographic factors, medical history, lifestyle, and diet. Habitual caffeine-containing coffee and tea intake was self-reported in cups/day and used to estimate caffeine intake. Between 97,369 and 445,786 participants with data also completed ≥1 of 7 self-administered cognitive functioning tests using a touchscreen system (2006–2010) or on home computers (2014). Multivariable regressions were used to examine the association between coffee, tea, or caffeine intake and cognition test scores. We also tested interactions between coffee, tea, or caffeine intake and a genetic-based caffeine-metabolism score (CMS) on cognitive function.

Results: After multivariable adjustment, reaction time, Pairs Matching, Trail Making test B, and symbol digit substitution, performance significantly decreased with consumption of 1 or more cups of coffee (all tests P-trend < 0.0001). Tea consumption was associated with poor performance on all tests (P-trend < 0.0001). No statistically significant CMS × tea, CMS × coffee, or CMS × caffeine interactions were observed.

Conclusions: Our findings, based on the participants of the UK Biobank, provide little support for habitual consumption of regular coffee or tea and caffeine in improving cognitive function. On the contrary, we observed decrements in performance with intakes of these beverages which may be a result of confounding. Whether habitual caffeine intake affects cognitive function therefore remains to be tested. *J Nutr* 2020;150:2164–2174.

Keywords: coffee, tea, caffeine, habitual, genotype, cognition, cohort

Introduction

Coffee and tea are among the most widely consumed beverages in the world and are major sources of dietary caffeine for most populations (1). Considerable evidence supports a role of caffeine in enhancing or maintaining cognitive function (2). Clinical studies suggest acute intakes of caffeine benefit tasks involving memory, concentration, and reaction time (RT) (3–11). However, studies of habitual caffeine intake and cognitive function, most feasibly done in an observational setting, have yielded mixed results (12). Observational studies may be biased by misclassification of caffeine "exposure" due to the use of self-reported coffee or tea cups as a unit of measure but also the known between-person variation in caffeine metabolism, which impacts duration of exposure to caffeine and its effects (13–18). For example, environmental and genetic factors impact the activity of CYP1A2, the enzyme responsible for >95% of caffeine metabolism (13–15). These factors, left unaccounted for, will magnify variability of response to dietary caffeine intake in the clinical or population setting and may explain the modest or inconsistent relation between caffeine and cognition in the literature. Genetic factors, in particular, may also provide causal and mechanistic insight to caffeine's role on cognition in populations, by separating the biological effects of caffeine from those of other compounds in caffeine-containing foods or from personal factors correlated with caffeine intake (17).

UK Biobank is a large population cohort of adults aged 37–73 y who underwent medical, sociodemographic, lifestyle, mental health, and cognitive assessment in 2006–2010. We used this valuable resource to examine the association between habitual coffee, tea, and caffeine intake on cognitive function

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whilst additionally accounting for genetic variation in caffeine metabolism.

Methods

Participants and protocol overview

In 2006–2010, the UK Biobank recruited over 502,633 participants aged 37–73 y at 22 centers across England, Wales, and Scotland (19). Participants completed questionnaires on sociodemographic factors, lifestyle, and medical history and a biospecimen collection period. A series of cognitive function tests was also administered via touchscreen whilst other tests were completed at home. Detailed study methods are provided in the **Supplementary Methods** and the order of operations is presented in **Supplemental Tables 1** and **2**. This study was covered by the generic ethical approval for UK Biobank studies from the National Research Ethics Service Committee North West–Haydock (approval letter dated 17 June 2011, Ref 11/NW/0382), and all study procedures were performed in accordance with the World Medical Association Declaration of Helsinki ethical principles for medical research.

Cognitive function testing (20)

Touchscreen tests at assessment centers (2006–2010).

Prospective memory (PM) and fluid intelligence (FI) tests were added part-way through the baseline assessment period. For PM, participants were given the following instructions: "At the end of the games we will show you 4 colored symbols and ask you to touch the blue square. However, to test your memory, we want you to actually touch the orange circle instead." Participants were scored as zero or 1, depending on whether they completed the task on first attempt or not. Cohen's kappa = 0.36 for PM has been reported elsewhere (21). For FI (or verbal-numerical reasoning), participants were presented with 13 verbal logic/reasoning-type questions and had to answer as many as they could within 2 min. Incorrect or unattempted questions were scored as zero. The total number of correct answers (max 13) was used for our analysis. The Cronbach α-coefficient for these items has been reported elsewhere as 0.62 (22). For Pairs Matching (Pairs), an episodic visual memory test, participants were shown 6 pairs of cards for 3 seconds, which were then turned over. Participants were asked to identify the matching pairs and the total number of errors made during this task was recorded. We restricted our analyses to individuals who finished the test and log(+1) transformed the number of errors for the analysis. For RT, participants completed a timed test of symbol matching. The score on this task was the mean response time in milliseconds (ms) across 4 trials which contained matching pairs. Potential outliers (N = 2751) were truncated to 100 (min) or 1000 (max) ms. Cronbach's α for this task has previously been reported as 0.85 (22).

Online tests on home computers (2014).

The Symbol Digit Substitution (SDS) test measures complex processing speed and involves matching numbers to a set of symbols. We used the number of correct substitutions for our analyses. Potential outliers (N = 236) were truncated to 1 (min) or 40 (max) correct substitutions. The Trail Making tests provide information on visual search, scanning, speed of processing, mental flexibility, and executive functions. Participants were asked to connect scattered circles containing a sequence of numbers (Trail A) and then to connect circles containing numbers or letters by alternating between them in ascending sequence (Trail B). We used the time taken to complete these tests for our analyses, and these data were log-transformed.

Coffee and tea assessment

The touchscreen questionnaire also included a dietary assessment of a range of common food and drink items. For coffee intake, participants were asked "How many cups of coffee do you drink each DAY?" (include decaffeinated coffee)." Participants either selected the number of cups, "<1," "Do not know," or "Prefer not to answer." Participants who reported drinking coffee were then asked, "What type of coffee do you usually drink?" and were able to select 1 of 3 prespecified responses including: "Decaffeinated coffee (any type)," "Instant coffee," or "Ground coffee (include espresso, filter etc.)." Because our primary exposure of interest was caffeine we restricted our primary analysis to "regular" (caffeine-containing) coffee; ~80% of coffee drinkers usually consumed regular. We defined regular coffee intake as follows: none, <1, 1, 2–3, 4–5, 6–7, and ≥8 cups/d for the current analysis. Participants reporting decaffeinated coffee intake were included in the "none" group and participants reporting coffee intake but missing information on type (0.4%) were included in a missing indicator variable. A similar question was asked about tea (include black and green tea), but no additional details on type of tea were collected. Tea was categorized for analysis as described for coffee above. Other dietary sources of caffeine were not captured by the questionnaire. We estimated total caffeine (mg/day) from regular coffee and tea by assigning each cup 75 mg and 40 mg of caffeine, respectively. Estimated caffeine consumption on a per body weight basis (i.e. mg/kg) was also derived. In a subset of 126,776 participants who also completed 2–5 24-h dietary recalls, the correlation (r) between their questionnaire and mean dietary-recall regular coffee and black/green tea intake was 0.73 and 0.74, respectively. Dietary recalls differentiated regular from decaffeinated black tea; only ~6% of black tea consumers drank the decaffeinated type.

Genetic data

All UK Biobank participants were genotyped using genome-wide arrays. Quality control and imputation to the HRC v1.1 and UK10K reference panels was performed centrally by the Wellcome Trust Centre for Human Genetics as described elsewhere (23). We excluded sample outliers based on heterozygosity and single-nucleotide polymorphism (SNP) missingness, participants with sex discrepancies between the self-reported and X-chromosome heterozygosity, and those potentially related to other participants, based on estimated kinship coefficients for all pairs of samples. We derived genetic "caffeine metabolism" scores (CMS_G) using 2 SNPs presenting with the largest effects sizes in genome-wide association studies (GWAS) of caffeine metabolites: rs2472297 (near *CYP1A2*) and rs6968554 (near *AHR*) (16), by summing the number of alleles multiplied by their β-coefficients. The latter were estimated by $z/(\text{sqrt}[p\{1-p\}])$ where z is the SNP z-score for the paraxanthine to caffeine ratio and p is the SNP minor allele frequency. Estimated β-coefficients for rs6968554 and rs2472297 were 17.58 and 21.58, respectively. CMS_G was calibrated such that it ranged from 0 to 4, with higher scores predicting faster caffeine metabolism. Because rs762551 (*CYP1A2*1F*) has been examined previously for interactions with coffee and disease outcomes (24), we conducted a separate analysis of this SNP. APOE carriers (ε4+) and noncarriers (ε4-) were defined using genotyped or imputed genotypes for SNPs rs429358 and rs7412. We limited the genetic analysis to unrelated individuals who self-reported as white British and had very similar ancestral backgrounds based on results of principal component analysis.

Potential confounders and other effect modifiers

During the UK Biobank Assessment Center visit participants completed a spirometry test ~20 min after cognitive function testing. The screening questionnaire for spirometry testing asked whether they had drunk caffeine within the last hour (herein referred to as "recent

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Supplemental Methods and Supplemental Tables 1–10 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.

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Abbreviations used: CMS, caffeine-metabolism score; FI, fluid intelligence; Pairs, Pairs Matching; PM, prospective memory; RT, reaction time; SDS, symbol digit substitution; SNP, single-nucleotide polymorphism; WHR, waist-to-hip ratio.

TABLE 1 Baseline characteristics of UK Biobank participants according to level of regular coffee consumption[1]

Characteristic	Regular coffee consumption, cups/day						
	None $N = 161{,}309$	<1 $N = 25{,}043$	1 $N = 71{,}503$	2–3 $N = 114{,}674$	4–5 $N = 49{,}204$	6–7 $N = 14{,}998$	≥8 $N = 7370$
Age, y	56.5 ± 8.1	56.5 ± 7.9	57.4 ± 8.0	57.0 ± 8.0	56.3 ± 8.0	56.0 ± 8.0	54.4 ± 8.0
Male, *n* (%)	63,291 (39.2)	11,694 (46.7)	31,786 (44.5)	55,482 (48.4)	26,054 (53.0)	8118 (54.1)	4406 (59.8)
Current smoker, *n* (%)	13,970 (8.7)	2198 (8.8)	5652 (7.9)	11,355 (9.9)	7520 (15.3)	3505 (23.4)	2697 (36.6)
BMI, kg/m^2	27.4 ± 4.9	27.1 ± 4.7	27.0 ± 4.6	27.2 ± 4.6	27.9 ± 4.7	28.2 ± 5.0	28.2 ± 5.1
Income, £<18,000, *n* (%)	32,416 (20.1)	4485 (17.9)	13,792 (19.3)	18,973 (16.6)	8223 (16.7)	3040 (20.3)	1716 (23.3)
College or university degree, *n* (%)	45,294 (28.1)	8729 (34.9)	24,310 (34.0)	42,691 (37.2)	16,699 (33.9)	4229 (28.2)	1898 (25.8)
Currently employed, *n* (%)	92,215 (57.2)	14,703 (58.7)	38,631 (54.0)	66,501 (58.0)	31,043 (63.1)	9589 (63.9)	4850 (65.8)
Townsend deprivation score	− 1.47 ± 2.99	− 1.48 ± 2.93	− 1.52 ± 2.94	− 1.57 ± 2.93	− 1.52 ± 2.95	− 1.22 ± 3.09	− 0.55 ± 3.37
Homeowner, *n* (%)	144,155 (89)	22,696 (90.6)	64,990 (90.9)	104,634 (91.2)	44,293 (90.0)	13,045 (87.0)	5913 (80.2)
Moderate to vigorous physical activity, minutes/week	76 ± 98	74 ± 92	78 ± 93	77 ± 93	75 ± 97	75 ± 109	81 ± 123
Hypertension, *n* (%)	84,210 (52.2)	13,378 (53.4)	38,779 (54.2)	61,448 (53.6)	26,502 (53.9)	8064 (53.8)	3635 (49.3)
Diabetes, *n* (%)	7643 (4.7)	1138 (4.5)	3119 (4.4)	5063 (4.4)	2545 (5.2)	824 (5.5)	452 (6.1)
Poor overall health rating, *n* (%)	7116 (4.4)	947 (3.8)	2326 (3.3)	3315 (2.9)	1713 (3.5)	703 (4.7)	600 (8.2)
Alcohol, drinks/week	0.99 ± 1.35	1.24 ± 1.49	1.25 ± 1.43	1.36 ± 1.43	1.39 ± 1.50	1.35 ± 1.64	1.32 ± 1.80
Fish, servings/week	0.32 ± 0.23	0.32 ± 0.22	0.33 ± 0.22	0.32 ± 0.22	0.31 ± 0.22	0.29 ± 0.22	0.29 ± 0.24
Red meat, servings/week	0.49 ± 0.31	0.51 ± 0.31	0.50 ± 0.30	0.52 ± 0.31	0.54 ± 0.32	0.56 ± 0.34	0.59 ± 0.38
Fruit, servings/week	3.06 ± 2.58	2.94 ± 2.36	3.13 ± 2.48	3.03 ± 2.43	2.80 ± 2.37	2.62 ± 2.41	2.53 ± 2.93
Vegetable, servings/week	0.81 ± 0.54	0.77 ± 0.50	0.81 ± 0.51	0.81 ± 0.52	0.79 ± 0.53	0.79 ± 0.58	0.78 ± 0.66
Decaffeinated coffee consumer, *n* (%)	67,642 (42)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tea, cups/day	4.0 ± 2.9	4.6 ± 2.5	3.9 ± 2.4	2.9 ± 2.3	2.1 ± 2.3	1.7 ± 2.6	2.0 ± 3.5
Coffee-/tea-derived caffeine, mg/day	161 ± 115	223 ± 100	231 ± 95	297 ± 93	410 ± 95	535 ± 109	790 ± 213
Recent caffeine drinking, *n* (%)	2602 (1.8)	357 (1.6)	1267 (1.9)	2321 (2.2)	1205 (2.7)	461 (3.4)	274 (4.1)
CMS_G[2]	1.69 ± 0.92	1.64 ± 0.92	1.67 ± 0.92	1.72 ± 0.92	1.80 ± 0.92	1.86 ± 0.93	1.90 ± 0.94
APOE ε4 carriers, *n* (%)	37,084 (28.5)	5893 (29.0)	16,497 (28.3)	26,776 (28.5)	11,392 (28.5)	3502 (28.7)	1649 (27.7)

[1]Data drawn from 2006–2010 for self-described white participants with information on coffee and tea intake and who completed ≥1 of the cognitive function tests. Values are mean ± SD or *n* (%). All characteristic values are significantly different across coffee categories ($P < 0.0001$) with the exception of APOE ($P = 0.47$).

[2]CMS_G: caffeine metabolism score; derived by summing the number of single-nucleotide polymorphism alleles multiplied by their β-coefficients and recalibrated such that it ranged from 0 to 4, with higher scores predicting faster caffeine metabolism.

TABLE 2 Baseline characteristics of UK Biobank participants according to level of tea consumption[1]

Characteristic	Tea consumption, cups/day						
	None $N = 65{,}808$	<1 $N = 13{,}657$	1 $N = 36{,}403$	2–3 $N = 128{,}122$	4–5 $N = 115{,}520$	6–7 $N = 54{,}087$	≥8 $N = 32{,}189$
Age, y	55.5 ± 8.2	55.6 ± 8.2	55.8 ± 8.3	56.9 ± 8.1	57.2 ± 7.9	57.3 ± 7.7	56.6 ± 7.8
Male, *n* (%)	28,444 (43.2)	6590 (48.3)	17,247 (47.4)	58,293 (45.5)	51,284 (44.4)	23,768 (43.9)	16,052 (49.9)
Current smoker, *n* (%)	8973 (13.6)	1710 (12.5)	3790 (10.4)	10,830 (8.5)	9974 (8.6)	5788 (10.7)	6061 (18.8)
BMI, kg/m^2	28.1 ± 5.3	27.6 ± 5.1	27.3 ± 4.8	27.1 ± 4.6	27.2 ± 4.6	27.3 ± 4.6	27.6 ± 4.8
Income, £<18,000, *n* (%)	12,583 (19.1)	2064 (15.1)	5462 (15.0)	21,423 (16.7)	22,075 (19.1)	11,424 (21.1)	7934 (24.7)
College or university degree, *n* (%)	19,810 (30.1)	6160 (45.1)	13,996 (38.5)	44,632 (34.8)	35,681 (30.9)	15,266 (28.2)	8586 (26.7)
Currently employed, *n* (%)	40,289 (61.2)	8586 (62.9)	22,490 (61.8)	73,910 (57.7)	64,612 (55.9)	30,426 (56.3)	18,198 (56.5)
Townsend deprivation score	− 1.24 ± 3.07	− 1.32 ± 3.01	− 1.44 ± 2.99	− 1.62 ± 2.91	− 1.63 ± 2.89	− 1.52 ± 2.94	− 1.02 ± 3.20
Homeowner, *n* (%)	57,790 (87.8)	12,318 (90.2)	32,855 (90.3)	117,082 (91.4)	105,083 (91.0)	48,601 (89.9)	27,418 (85.2)
Moderate to vigorous physical activity, minutes/week	73 ± 99	67 ± 82	74 ± 91	75 ± 91	78 ± 96	79 ± 103	82 ± 112
Hypertension, *n* (%)	34,629 (52.6)	7082 (51.9)	18,788 (51.6)	68,141 (53.2)	62,114 (53.8)	29,228 (54.0)	16,903 (52.5)
Diabetes, *n* (%)	3875 (5.9)	690 (5.1)	1661 (4.6)	5568 (4.4)	5037 (4.4)	2399 (4.4)	1661 (5.2)
Poor overall health rating, *n* (%)	3211 (4.9)	515 (3.8)	1210 (3.3)	3770 (3.0)	3845 (3.3)	2191 (4.1)	2086 (6.5)
Alcohol, drinks/week	1.21 ± 1.58	1.38 ± 1.60	1.36 ± 1.51	1.27 ± 1.42	1.15 ± 1.34	1.07 ± 1.31	1.08 ± 1.51
Fish, servings/week	0.30 ± 0.23	0.31 ± 0.22	0.32 ± 0.22	0.33 ± 0.22	0.33 ± 0.22	0.32 ± 0.23	0.31 ± 0.24
Red, meat servings/week	0.50 ± 0.33	0.51 ± 0.32	0.50 ± 0.31	0.50 ± 0.30	0.51 ± 0.31	0.52 ± 0.32	0.55 ± 0.34
Fruit, servings/week	2.85 ± 2.61	2.87 ± 2.56	2.99 ± 2.45	3.05 ± 2.40	3.07 ± 2.43	3.03 ± 2.51	2.96 ± 2.80
Vegetable, servings/week	0.79 ± 0.58	0.78 ± 0.56	0.80 ± 0.54	0.80 ± 0.51	0.80 ± 0.51	0.80 ± 0.51	0.82 ± 0.60
Regular coffee, cups/day	2.8 ± 2.7	2.8 ± 2.4	2.3 ± 2.1	1.7 ± 1.7	1.2 ± 1.5	0.9 ± 1.4	1.0 ± 2.0
Coffee-/tea-derived caffeine, mg/day	210 ± 204	229 ± 177	212 ± 154	226 ± 127	265 ± 111	320 ± 109	466 ± 178
Recent caffeine drinking, *n* (%)	1337 (2.2)	283 (2.2)	729 (2.2)	2377 (2.0)	2118 (2.0)	1030 (2.1)	721 (2.5)
CMS_G[2]	1.71 ± 0.93	1.66 ± 0.92	1.65 ± 0.92	1.67 ± 0.92	1.72 ± 0.92	1.79 ± 0.92	1.86 ± 0.93
APOE ε4 carriers, *n* (%)	15,279 (28.6)	3238 (28.6)	8559 (28.7)	29,520 (28.2)	26,619 (28.5)	12,576 (28.9)	7350 (28.5)

[1]Data drawn from 2006–2010 for self-described white participants with information on coffee and tea intake and who completed ≥1 of the cognitive function tests. Values are mean (±SD) unless stated otherwise. All characteristic values are significantly different across tea categories ($P < 0.0001$) with the exception of APOE ($P = 0.11$).
[2]CMS_G: caffeine metabolism score; derived by summing the number of single-nucleotide polymorphism alleles multiplied by their β-coefficients and recalibrated such that it ranged from 0 to 4, with higher scores predicting faster caffeine metabolism.

caffeine drinking"); participants replied yes or no. No data on recent caffeine drinking was collected for cognitive function tests completed at home. Information on several other covariates functioning as potential confounders in observation analysis of caffeine and cognitive function were also collected as described in detail previously (19, 25). For the current analysis we considered baseline smoking status, Townsend deprivation index (higher scores represent higher deprivation), education, income, homeownership, physical activity, race, employment status, self-rated health, alcohol intake, water intake, fish intake, red meat intake, fruit intake, and vegetable intake. The time when cognitive function testing took place at the center was recorded for only the PM test and was therefore also used as a proxy time for FI, Pairs, and RT. For the SDS and Trail tests, completed online at home, the time initiated was recorded.

Statistical analysis

A total of 493,944 participants had information on coffee and tea intake and completed ≥1 of the cognitive function tests. Because some cognitive tasks were added at different stages of baseline assessment or not until 2014, the number of participants varies across tests (see Supplemental Tables 1 and 2 for detailed sample sizes). We excluded 21,744 who self-reported neurological disease at baseline that could directly affect cognitive function leaving ≤472,200 participants for analysis (21). Our main analysis was restricted to the 445,786 self-described white participants to, in part, facilitate comparison with the results of genetic analysis, which were limited to white British ancestry. Nonwhites included Asian, black, Chinese, mixed, or other and together constituted 6% of the UK Biobank. Due to the relatively smaller sample size for each race, known race differences in genetics and coffee/tea drinking behaviors, we excluded nonwhites from the current analysis.

We examined the association between habitual regular coffee consumption (7 categories, nondrinkers the referent group) and all cognitive tests using linear or logistic (PM only) regressions adjusting for age and sex (model 1). In multivariable regressions we further adjusted for baseline smoking (never, past, current: <10, 10–19, ≥20 cigarettes/d), fasting status (0–1 h, 3–4 h, ≥5 h), Townsend index (quartiles), education (college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC equivalent, or other professional qualifications), income (4 levels), homeownership (yes, no), physical activity (quartiles of moderate/vigorous activity minutes/week), employment status (employed, retired, other), waist-to-hip ratio (WHR), self-reported health (excellent, good, fair, poor), and intakes of alcohol, water, fish, red meat, fruits, and vegetables (quartiles of servings/week) (model 2). Missing indicator variables were constructed to maximize sample size (see Supplemental Table 1 for sample size per covariate). A third multivariable regression model further adjusted for habitual tea intake (7 categories) (model 3). A linear test for trend was used to assess whether cognitive scores were progressively lower or higher with increasing coffee intake by modeling coffee as a continuous variable (cups/day, with intakes exceeding 15 cups/d re-coded to 15 cups/d). The same statistical analysis described above for regular coffee was also applied to the analysis of habitual tea and habitual caffeine intake. We additionally examined decaffeinated coffee separately as a negative control to support our hypothesis that caffeine per se associates with better cognitive performance. In sensitivity analysis we further adjusted models separately for recent caffeine drinking, exam date, and diabetes and hypertension status; and excluded decaffeinated consumers from the regular coffee analysis

TABLE 3 Associations between regular coffee consumption and cognitive function tests in the UK Biobank

Cups/day	N	Score[6]	Model 1[1]		Model 2[2]		Model 3[3]	
			β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Fluid Intelligence[4]								
0	50,782	5.98 ± 2.11	Reference		Reference		Reference	
<1	8455	6.33 ± 2.09	0.32 (0.28, 0.37)	<0.0001	0.14 (0.09, 0.18)	<0.0001	0.15 (0.11, 0.20)	<0.0001
1	24,440	6.12 ± 2.09	0.14 (0.11, 0.17)	<0.0001	− 0.03 (−0.06, −0.002)	0.04	− 0.03 (−0.06, 0.002)	0.06
2–3	38,486	6.29 ± 2.11	0.29 (0.26, 0.32)	<0.0001	0.03 (0.01, 0.06)	0.007	0.01 (−0.02, 0.03)	0.60
4–5	16,265	6.28 ± 2.14	0.25 (0.22, 0.29)	<0.0001	0.10 (0.07, 0.13)	<0.0001	0.03 (−0.0006, 0.07)	0.05
6–7	4823	6.08 ± 2.10	0.05 (−0.01, 0.12)	0.09	0.03 (−0.02, 0.09)	0.23	− 0.06 (−0.11, −0.0009)	0.05
≥8	2373	5.96 ± 2.17	− 0.12 (−0.21, −0.04)	0.005	0.04 (−0.03, 0.12)	0.27	− 0.04 (−0.12, 0.03)	0.27
Cups/day, linear trend			0.02 (0.02, 0.03)	<0.0001	0.011 (0.006, 0.02)	<0.0001	− 0.003 (−0.008, 0.002)	0.28
Reaction Time[5]								
0	159,924	554 ± 108	Reference		Reference		Reference	
<1	24,915	550 ± 106	− 2.53 (−3.89, −1.18)	0.0003	− 0.25 (−1.60, 1.09)	0.71	− 0.89 (−2.24, 0.45)	0.19
1	70,974	557 ± 108	0.90 (0.01, 1.80)	0.05	3.25 (2.35, 4.15)	<0.0001	3.05 (2.15, 3.95)	<0.0001
2–3	113,869	554 ± 107	− 0.97 (−1.74, −0.20)	0.01	2.60 (1.82, 3.38)	<0.0001	3.26 (2.47, 4.05)	<0.0001
4–5	48,930	549 ± 105	− 1.66 (−2.70, −0.63)	0.002	0.87 (−0.16, 1.90)	0.10	2.64 (1.58, 3.71)	<0.0001
6–7	14,885	551 ± 106	1.45 (−0.26, 3.16)	0.10	1.24 (−0.46, 2.94)	0.15	3.67 (1.94, 5.41)	<0.0001
≥8	7298	547 ± 106	4.96 (2.57,7.34)	<0.0001	0.41 (−1.98, 2.80)	0.74	3.06 (0.64, 5.49)	0.01
Cups/day, linear trend			0.09 (−0.06, 0.24)	0.27	0.17 (0.02, 0.32)	0.03	0.56 (0.40, 0.72)	<0.0001
[5]Pairs Matching								
0	157,997	1.46 ± 0.62	Reference		Reference		Reference	
<1	24,648	1.46 ± 0.63	− 0.001 (−0.009, 0.007)	0.83	0.012 (0.004, 0.020)	0.004	0.007 (−0.001, 0.016)	0.08
1	70,070	1.48 ± 0.63	0.012 (0.007, 0.018)	<0.0001	0.022 (0.016, 0.027)	<0.0001	0.019 (0.014, 0.025)	<0.0001
2–3	112,541	1.46 ± 0.63	0.001 (−0.003, 0.006)	0.57	0.017 (0.012, 0.022)	<0.0001	0.020 (0.016, 0.025)	<0.0001
4–5	48,415	1.44 ± 0.62	− 0.015 (−0.021, −0.009)	<0.0001	0.0003 (−0.006, 0.007)	0.93	0.013 (0.006, 0.019)	0.0001
6–7	14,745	1.43 ± 0.62	− 0.024 (−0.034, −0.013)	<0.0001	− 0.013 (−0.024, −0.003)	0.01	0.005 (−0.005, 0.016)	0.32
≥8	7223	1.42 ± 0.63	− 0.011 (−0.026,0.003)	0.13	− 0.011 (−0.026, 0.004)	0.14	0.010 (−0.005, 0.024)	0.20
Cups/day, linear trend			− 0.003 (−0.004, −0.002)	<0.0001	− 0.001 (−0.002, 0.0001)	0.10	0.002 (0.001, 0.003)	<0.0001
Symbol Digit Substitution[4]								
0	37,537	19.9 ± 5.3	Reference		Reference		Reference	
<1	6805	19.7 ± 5.2	− 0.14 (−0.26, −0.02)	0.02	− 0.25 (−0.37, −0.14)	<0.0001	− 0.19 (−0.31, −0.07)	0.002
1	18,392	19.5 ± 5.1	− 0.09 (−0.17, −0.01)	0.03	− 0.22 (−0.30, −0.14)	<0.0001	− 0.21 (−0.29, −0.13)	<0.0001
2–3	30,420	19.7 ± 5.1	0.07 (−0.003, 0.14)	0.06	− 0.15 (−0.22, −0.08)	<0.0001	− 0.22 (−0.29, −0.15)	<0.0001
4–5	12,139	20.0 ± 5.1	0.16 (0.06, 0.26)	0.001	− 0.01 (−0.11, 0.08)	0.79	− 0.18 (−0.27, −0.08)	0.0004
6–7	3305	19.8 ± 5.2	− 0.10 (−0.26, 0.07)	0.24	− 0.08 (−0.24, 0.08)	0.35	− 0.29 (−0.46, −0.13)	0.001
≥8	1397	19.9 ± 5.2	− 0.39 (−0.64, −0.14)	0.002	− 0.20 (−0.45, 0.04)	0.10	− 0.43 (−0.68, −0.19)	0.001
Cups/day, linear trend			0.01 (−0.005, 0.02)	0.20	− 0.005 (−0.02, 0.009)	0.48	− 0.04 (−0.06, −0.03)	<0.0001
Trail A[5]								
0	32,948	3.61 ± 0.33	Reference		Reference		Reference	
<1	6019	3.61 ± 0.33	0.002 (−0.006, 0.011)	0.62	0.007 (−0.001, 0.015)	0.11	0.003 (−0.005, 0.012)	0.44
1	16,183	3.62 ± 0.32	0.001 (−0.005, 0.006)	0.81	0.006 (0.0003, 0.012)	0.04	0.005 (−0.001, 0.010)	0.11
2–3	26,721	3.60 ± 0.32	− 0.011 (−0.016, −0.006)	<0.0001	− 0.001 (−0.006, 0.004)	0.77	0.002 (−0.003, 0.008)	0.35
4–5	10,761	3.59 ± 0.33	− 0.013 (−0.020, −0.007)	0.0001	− 0.005 (−0.011, 0.002)	0.19	0.004 (−0.003, 0.011)	0.23
6–7	2907	3.60 ± 0.33	− 0.001 (−0.013, 0.011)	0.88	− 0.001 (−0.012, 0.011)	0.90	0.012 (0.00009, 0.024)	0.05
≥8	1252	3.59 ± 0.33	0.013 (−0.005, 0.030)	0.15	0.006 (−0.011, 0.024)	0.47	0.020 (0.003, 0.038)	0.02
Cups/day, linear trend			− 0.002 (−0.003, −0.001)	0.002	− 0.001 (−0.002, 0.0003)	0.16	0.001 (0.0002, 0.002)	0.02
Trail B[5]								
0	32,948	4.13 ± 0.34	Reference		Reference		Reference	
<1	6018	4.13 ± 0.33	− 0.002 (−0.011, 0.006)	0.57	0.006 (−0.002, 0.015)	0.13	0.002 (−0.006, 0.011)	0.58
1	16,183	4.15 ± 0.34	0.007 (0.001, 0.013)	0.02	0.016 (0.011, 0.022)	<0.0001	0.015 (0.009, 0.020)	<0.0001
2–3	26,720	4.14 ± 0.33	− 0.009 (−0.014, −0.004)	0.001	0.007 (0.002, 0.012)	0.004	0.011 (0.006, 0.016)	<0.0001
4–5	10,761	4.12 ± 0.34	− 0.014 (−0.021, −0.008)	<0.0001	− 0.003 (−0.010, 0.004)	0.38	0.008 (0.001, 0.014)	0.03
6–7	2907	4.13 ± 0.34	− 0.00002 (−0.012, 0.012)	0.99	− 0.005 (−0.016, 0.007)	0.40	0.010 (−0.001, 0.022)	0.08
≥8	1252	4.14 ± 0.35	0.038 (0.020, 0.055)	<0.0001	0.019 (0.002, 0.036)	0.03	0.035 (0.018, 0.053)	<0.0001
Cups/day, linear trend			− 0.001 (−0.002, 0.00003)	0.06	− 0.0003 (−0.001, 0.001)	0.53	0.002 (0.001, 0.003)	<0.0001

(*Continued*)

TABLE 3 (*Continued*)

Cups/day	N	Score[6]	Model 1[1]		Model 2[2]		Model 3[3]	
			β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Prospective Memory Test[4]								
	N	% correct	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
0	51,947	78.3	Reference		Reference		Reference	
<1	8590	82.8	1.33 (1.25, 1.41)	<0.0001	1.20 (1.12, 1.27)	<0.0001	1.21 (1.14, 1.29)	<0.0001
1	24,963	78.9	1.07 (1.03, 1.11)	0.001	0.98 (0.94, 1.02)	0.25	0.99 (0.95, 1.02)	0.45
2–3	39,203	79.9	1.12 (1.08, 1.16)	<0.0001	0.97 (0.94, 1.01)	0.110	0.96 (0.92, 0.99)	0.01
4–5	16,545	81.2	1.18 (1.12, 1.23)	<0.0001	1.07 (1.02, 1.12)	0.007	1.01 (0.96, 1.06)	0.69
6–7	4917	80.1	1.09 (1.01, 1.17)	0.02	1.06 (0.98, 1.15)	0.13	0.98 (0.91, 1.06)	0.62
≥8	2456	78.8	0.92 (0.84, 1.02)	0.12	1.02 (0.92, 1.13)	0.70	0.94 (0.85, 1.05)	0.26
Cups/day, linear trend			1.01 (1.01, 1.02)	0.001	1.00 (1.00, 1.01)	0.30	0.99 (0.99, 1.00)	0.03

[1]Model 1: adjusted for age and sex.
[2]Model 2: adjusted for age, sex, smoking, Townsend deprivation index, education, income, employment status, homeownership, self-reported health, waist-to-hip ratio, physical activity, fasting time and intakes of alcohol, water, fish, red meat, fruit, and vegetables.
[3]Model 3: model 2 adjusted for tea consumption.
[4]Positive β-coefficients for FI (difference in 13-point score) and SDS (difference in number of correct substitutions) and OR >1 for PM (correct on first attempt) correspond to higher performance compared with nondrinkers (0 cups/day).
[5]Negative β-coefficients for Pairs [difference in (log-transformed) number of errors], RT (difference in time, seconds, to respond), Trails A and Trails B [difference in (log transformed) time to complete] correspond to higher performance compared with nondrinkers (0 cups/d).
[6]Data are raw mean ± SD scores of each cognitive function test stratified by regular coffee consumption.
FI, fluid intelligence; Pairs, Pairs Matching; PM, prospective memory; RT, reaction time; SDS, symbol digit substitution.

(impacting the "none" group only) and vice versa. Statistical significance was defined as $P < 0.004$; and reflects an α-correction for 7 cognitive function tests and 2 independent exposures (regular coffee and tea).

We screened beverage interactions with age (<55 or ≥55 y), sex (male or female), education (university/college degree or less), smoking (never, past, current), exam time (5 time categories), *APOE* ε4 carrier status, and CMS_G by including in multivariable regression models the cross-product term of beverage intake with the interacting variable. Significant interactions were defined as $P < 0.0005$, after applying a correction for 98 tests (7 cognitive function tests, 6 potential modifiers, and 2 independent exposures), and the nature of these interactions was described by stratified analysis.

Results

Participant characteristics

Descriptive characteristics across categories of habitual regular coffee and tea consumption are presented in Tables 1 and 2. Compared with regular coffee abstainers, regular coffee drinkers (>0 cups/d) were more likely to be male, and consume more alcohol and red meat. Heavy coffee drinkers were younger, drank less tea, and were more likely to be male, current smokers, to have diabetes, poor self-reported health and higher measures of adiposity, and less likely to have a college or university degree compared with light drinkers. They were also more likely to report drinking caffeine close to the time of cognitive function testing at the center. Tea drinkers were older, more likely to be male, have a lower BMI, consume more fish, red meat, fruits, and vegetables, and less likely to have diabetes compared with tea abstainers. Heavy tea drinkers were more likely to be current smokers, to consume less alcohol and coffee but more red meat, to have a lower income and poor self-reported health, engage in more moderate/vigorous exercise, and less likely to have a college or university degree and own their home compared with light tea drinkers. Characteristics of the unrelated (white) British ancestry subgroup according to CMS_G are presented in **Supplemental Table 3**. As anticipated, CMS_G was significantly associated with habitual coffee, tea, and total caffeine consumption ($P < 0.0001$); with higher CMS_G associated with higher intakes. Those with higher CMS_G were also more likely to consume regular coffee and to be recent caffeine drinkers near the time of cognitive function testing. BMI, WHR, number of alcoholic drinks, and servings of meat and fruit also increased with CMS_G.

Habitual regular coffee intake and cognitive function

With the exception of RT, habitual regular coffee consumption was associated with better performance on all cognitive function tests in crude models with no apparent dose-response relation (Table 3). All associations were attenuated with multivariable (model 2) adjustment and largely abolished, if not reversed, when additionally adjusted for tea consumption (model 3). RT, Pairs, Trails B, and SDS performance significantly decreased with consumption of ∼1 or more cups of coffee (P-trend < 0.0001). Similar results were observed when excluding decaffeinated coffee consumers from the referent group. Further adjustment for recent caffeine drinking (FI, RT, Pairs, and PM only), exam time, and disease status had negligible impact on results. Consumption of decaffeinated coffee was associated with dose-response improvements in Pairs (P-trend < 0.0001) and Trails B (P-trend < 0.0001) performance but results were nonsignificant when excluding regular coffee consumers.

Habitual tea intake and cognitive function

Consumption of 1 or more cups of tea per day was significantly associated with dose-response decreases in performance on all cognitive function tests compared with no tea consumption (Table 4). Results were similar when further adjusted for recent caffeine drinking, exam time, and disease status.

Habitual caffeine intake and cognitive function

Caffeine intake (derived from regular coffee and tea) exceeding 100 mg/d was significantly associated with impaired performance on all cognitive function tests compared with noncaffeine consumers in multivariable models (all P-trend < 0.001, **Supplemental Table 4**). We observed similar decreases in test performances when caffeine intake was expressed relative to weight mg/(kg · d) (data not shown). Results were similar

TABLE 4 Associations between tea consumption and cognitive function tests in the UK Biobank

Cups/day	N	Score[6]	Model 1[1]		Model 2[2]		Model 3[3]	
			β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Fluid Intelligence[4]								
0	21,274	6.17 ± 2.14	Reference		Reference		Reference	
<1	4355	6.79 ± 2.13	0.61 (0.54, 0.68)	<0.0001	0.25 (0.19,0.31)	<0.0001	0.24 (0.18, 0.30)	<0.0001
1	11,718	6.36 ± 2.13	0.19 (0.14, 0.23)	<0.0001	− 0.04 (−0.09, −0.0007)	0.05	− 0.05 (−0.09, −0.003)	0.04
2–3	41,643	6.23 ± 2.10	0.08 (0.04, 0.11)	<0.0001	− 0.10 (−0.14, −0.07)	<0.0001	− 0.11 (−0.14, −0.08)	<0.0001
4–5	38,111	6.06 ± 2.10	− 0.08 (−0.12, −0.05)	<0.0001	− 0.16 (−0.19, −0.13)	<0.0001	− 0.17 (−0.20, −0.14)	<0.0001
6–7	18,040	5.99 ± 2.07	− 0.15 (−0.19, −0.11)	<0.0001	− 0.15 (−0.19, −0.11)	<0.0001	− 0.16 (−0.20, −0.12)	<0.0001
≥8	10,822	5.80 ± 2.10	− 0.37 (−0.41, −0.32)	<0.0001	− 0.23 (−0.28, −0.19)	<0.0001	− 0.24 (−0.29, −0.20)	<0.0001
Cups/day, linear trend			− 0.05 (−0.06, −0.05)	<0.0001	− 0.03 (−0.03, −0.02)	<0.0001	− 0.03 (−0.03, −0.03)	<0.0001
Reaction Time[5]								
0	65,281	547 ± 105	Reference		Reference		Reference	
<1	13,581	543 ± 103	− 3.20 (−5.08, −1.32)	0.0008	0.61 (−1.25, 2.47)	0.52	0.48 (−1.38, 2.35)	0.61
1	36,123	546 ± 104	− 1.05 (−2.35, 0.25)	0.11	2.36 (1.07, 3.66)	0.0004	2.24 (0.93, 3.54)	0.0008
2–3	127,074	553 ± 107	1.07 (0.11, 2.03)	0.03	4.19 (3.23, 5.15)	<0.0001	4.33 (3.34, 5.32)	<0.0001
4–5	114,519	557 ± 108	3.14 (2.16, 4.12)	<0.0001	5.04 (4.06, 6.02)	<0.0001	5.62 (4.60, 6.64)	<0.0001
6–7	53,608	559 ± 108	4.99 (3.83, 6.15)	<0.0001	5.83 (4.67, 6.99)	<0.0001	6.70 (5.50, 7.91)	<0.0001
≥8	31,856	558 ± 109	7.74 (6.38, 9.10)	<0.0001	5.48 (4.12, 6.84)	<0.0001	6.50 (5.10, 7.90)	<0.0001
Cups/day, linear trend			0.95 (0.83, 1.06)	<0.0001	0.61 (0.50, 0.73)	<0.0001	0.72 (0.61, 0.84)	<0.0001
Pairs Matching[5]								
0	64,591	1.41 ± 0.62	Reference		Reference		Reference	
<1	13,436	1.40 ± 0.63	− 0.015 (−0.026, −0.003)	0.01	0.004 (−0.007, 0.016)	0.47	0.002 (−0.009, 0.013)	0.70
1	35,783	1.44 ± 0.63	0.019 (0.011, 0.027)	<0.0001	0.030 (0.022, 0.038)	<0.0001	0.027 (0.019, 0.035)	<0.0001
2–3	125,622	1.47 ± 0.62	0.036 (0.030, 0.042)	<0.0001	0.044 (0.038, 0.050)	<0.0001	0.042 (0.036, 0.0498)	<0.0001
4–5	113,091	1.48 ± 0.62	0.042 (0.036, 0.048)	<0.0001	0.046 (0.040, 0.052)	<0.0001	0.046 (0.040, 0.053)	<0.0001
6–7	52,892	1.48 ± 0.62	0.045 (0.038, 0.052)	<0.0001	0.046 (0.039, 0.053)	<0.0001	0.048 (0.040, 0.055)	<0.0001
≥8	31,407	1.48 ± 0.63	0.052 (0.043, 0.060)	<0.0001	0.046 (0.038, 0.054)	<0.0001	0.048 (0.040, 0.057)	<0.0001
Cups/day, linear trend			0.006 (0.005, 0.006)	<0.0001	0.004 (0.004, 0.005)	<0.0001	0.005 (0.004, 0.005)	<0.0001
Symbol Digit Substitution[4]								
0	16,104	20.3 ± 5.2	Reference		Reference		Reference	
<1	4287	20.4 ± 5.1	0.14 (−0.01, 0.30)	0.08	− 0.10 (−0.25, 0.05)	0.20	− 0.09 (−0.24, 0.06)	0.24
1	9859	20.2 ± 5.1	0.07 (−0.04, 0.19)	0.22	− 0.12 (−0.23, −0.004)	0.04	− 0.11 (−0.23, 0.002)	0.05
2–3	33,407	19.8 ± 5.1	− 0.14 (−0.22, −0.05)	0.002	− 0.30 (−0.39, −0.22)	<0.0001	− 0.31 (−0.40, −0.22)	<0.0001
4–5	27,793	19.5 ± 5.2	− 0.37 (−0.46, −0.28)	<0.0001	− 0.45 (−0.54, −0.37)	<0.0001	− 0.48 (−0.57, −0.39)	<0.0001
6–7	12,368	19.3 ± 5.2	− 0.54 (−0.65, −0.43)	<0.0001	− 0.54 (−0.64, −0.43)	<0.0001	− 0.58 (−0.69, −0.47)	<0.0001
≥8	6822	19.4 ± 5.3	− 0.72 (−0.86, −0.59)	<0.0001	− 0.61 (−0.74, −0.48)	<0.0001	− 0.66 (−0.79, −0.53)	<0.0001
Cups/day, linear trend			− 0.09 (−0.10, −0.08)	<0.0001	− 0.07 (−0.08, −0.06)	<0.0001	− 0.08 (−0.09, −0.07)	<0.0001
Trail A[5]								
0	14,356	3.58 ± 0.32	Reference		Reference		Reference	
<1	3828	3.57 ± 0.31	− 0.009 (−0.020, 0.002)	0.11	0.002 (−0.008, 0.013)	0.66	0.003 (−0.008, 0.013)	0.63
1	8722	3.59 ± 0.32	0.004 (−0.004, 0.012)	0.34	0.013 (0.004, 0.021)	0.002	0.013 (0.005, 0.021)	0.001
2–3	29,394	3.61 ± 0.32	0.014 (0.008, 0.020)	<0.0001	0.020 (0.014, 0.027)	<0.0001	0.021 (0.015, 0.028)	<0.0001
4–5	24,291	3.62 ± 0.33	0.027 (0.021, 0.033)	<0.0001	0.029 (0.022, 0.035)	<0.0001	0.030 (0.024, 0.037)	<0.0001
6–7	10,788	3.63 ± 0.33	0.036 (0.028, 0.043)	<0.0001	0.033 (0.025, 0.040)	<0.0001	0.035 (0.027, 0.043)	<0.0001
≥8	5992	3.62 ± 0.33	0.037 (0.028, 0.046)	<0.0001	0.030 (0.020, 0.039)	<0.0001	0.032 (0.022, 0.041)	<0.0001
Cups/day, linear trend			0.005 (0.004, 0.006)	<0.0001	0.004 (0.003, 0.005)	<0.0001	0.004 (0.003, 0.005)	<0.0001
Trail B[5]								
0	14,356	4.10 ± 0.33	Reference		Reference		Reference	
<1	3828	4.08 ± 0.32	− 0.024 (−0.035, −0.013)	<0.0001	− 0.004 (−0.015, 0.007)	0.46	− 0.004 (−0.014, 0.007)	0.50
1	8722	4.11 ± 0.33	0.004 (−0.004, 0.013)	0.29	0.020 (0.012, 0.028)	<0.0001	0.020 (0.012, 0.028)	<0.0001
2–3	29,393	4.13 ± 0.33	0.011 (0.005, 0.018)	0.0003	0.025 (0.019, 0.031)	<0.0001	0.025 (0.019, 0.031)	<0.0001
4–5	24,290	4.15 ± 0.34	0.027 (0.021, 0.033)	<0.0001	0.034 (0.028, 0.040)	<0.0001	0.035 (0.029, 0.042)	<0.0001
6–7	10,788	4.16 ± 0.34	0.040 (0.032, 0.047)	<0.0001	0.039 (0.031, 0.047)	<0.0001	0.041 (0.034, 0.049)	<0.0001
≥8	5992	4.15 ± 0.35	0.045 (0.036, 0.055)	<0.0001	0.036 (0.027, 0.045)	<0.0001	0.039 (0.030, 0.048)	<0.0001
Cups/day, linear trend			0.006 (0.005, 0.007)	<0.0001	0.005 (0.004, 0.005)	<0.0001	0.005 (0.004, 0.006)	<0.0001

(*Continued*)

TABLE 4 (*Continued*)

Cups/day	N	Score[6]	Model 1[1]		Model 2[2]		Model 3[3]	
			β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Prospective Memory Test[4]								
	N	% correct	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
0	21,672	81.0	Reference		Reference		Reference	
<1	4418	85.5	1.39 (1.27, 1.52)	<0.0001	1.16 (1.05, 1.27)	0.002	1.15 (1.04, 1.27)	0.003
1	11,931	81.6	1.05 (0.99, 1.11)	0.10	0.92 (0.87, 0.98)	0.01	0.93 (0.87, 0.98)	0.01
2–3	42,405	79.5	0.96 (0.92, 1.00)	0.07	0.86 (0.82, 0.90)	<0.0001	0.86 (0.82, 0.90)	<0.0001
4–5	38,951	78.6	0.92 (0.88, 0.96)	<0.0001	0.86 (0.82, 0.90)	<0.0001	0.85 (0.81, 0.89)	<0.0001
6–7	18,453	78.1	0.89 (0.85, 0.94)	<0.0001	0.86 (0.82, 0.91)	<0.0001	0.84 (0.80, 0.89)	<0.0001
≥8	11,155	76.6	0.79 (0.75, 0.84)	<0.0001	0.83 (0.79, 0.88)	<0.0001	0.82 (0.77, 0.87)	<0.0001
Cups/day, linear trend			0.97 (0.97, 0.98)	<0.0001	0.98 (0.98, 0.99)	<0.0001	0.98 (0.97, 0.98)	<0.0001

[1]Model 1: adjusted for age and sex.

[2]Model 2: adjusted for age, sex, smoking, Townsend deprivation index, education, income, employment status, homeownership, self-reported health, waist-to-hip ratio, physical activity, fasting time and intakes of alcohol, water, fish, red meat, and fruit and vegetables.

[3]Model 3: model 2 adjusted for regular coffee consumption.

[4]Positive β-coefficients for FI (difference in 13-point score) and SDS (difference in number of correct substitutions) and OR >1 for PM (correct on first attempt) correspond to higher performance compared with nondrinkers (0 cups/d).

[5]Negative β-coefficients for Pairs [difference in (log-transformed) number of errors], RT (difference in time, seconds, to respond), Trails A and Trails B [difference in (log transformed) time to complete] correspond to higher performance compared with nondrinkers (0 cups/d).

[6]Data are raw mean ± SD scores of each cognitive function test stratified by tea consumption.

FI, fluid intelligence; Pairs, Pairs Matching; PM, prospective memory; RT, reaction time; SDS, symbol digit substitution.

when further adjusting for recent caffeine drinking, exam time, and disease status.

Interactions with age, sex, education, smoking, exam time, and *APOE*

Significant age × coffee, age × tea, and age × caffeine interactions ($P < 0.0005$) were observed for all cognitive function tests but age-stratified analysis suggested no consistent patterns (**Supplemental Tables 5–7**). For example, an adverse impact of regular coffee intake on FI and RT performance was more pronounced among those aged <55 y than among those aged ≥55 y; whereas an adverse impact of coffee on SDS was more pronounced among those aged ≥55 y.

Significant sex × caffeine interactions ($P \leq 0.0004$) were observed for Pairs and PM tests, whereby greater decrements with increased caffeine intake were observed among women than among men. A significant sex × tea interaction for FI ($P = 0.0002$) was also observed but difficult to interpret upon stratification. Significant smoking × caffeine interactions were observed for FI, PM, and Pairs ($P < 0.0003$, **Supplemental Table 8**): the negative impact of caffeine intake on these tests was restricted to never and past smokers. A similar pattern of interaction on Pairs was observed with regular coffee consumption ($P < 0.0001$). Significant exam time × coffee and exam time × caffeine interactions were observed for FI ($P < 0.0005$): greater impairment in FI with coffee or caffeine intake was observed when this test was performed earlier than later in the day.

Caffeine genetic analysis

CMS_G was nominally associated with decreased performance on RT ($P = 0.02$), Trail A ($P = 0.005$), and Trail B ($P = 0.01$) tests. Associations between regular coffee consumption and cognitive function stratified by CMS_G are presented in **Table 5**. For Trail A and B tests, coffee intake generally presented greater and dose-response decrements in performance among those with the highest CMS_G than among those with lower CMS_G but tests for interaction were only nominally significant ($P < 0.05$).

Nominally significant CMS_G × caffeine and CMS_G × tea interactions for FI were observed ($P < 0.05$); likely driven by a weaker (yet significant) relation between caffeine/tea and FI among those with a higher CMS_G (**Supplemental Table 9**). We also examined interactions with *CYP1A2* rs762551 (*CYP1A2*1F*). A nominal rs762551 × coffee ($P = 0.02$) interaction for Pairs was observed whereby those with the AA genotype (fast metabolizer genotype) presented with greater decrements in performance with coffee intake than those with CC or AC genotypes (**Supplemental Table 10**). Similar results were observed when statistical models were further adjusted for 20 principal components.

Discussion

The current analysis of over 400,000 participants of the UK Biobank provides little support for the habitual consumption of the major contributors of caffeine in the diet, coffee and tea, in improving cognitive function. On the contrary, we observed decrements in cognitive function with intakes of these beverages which we believe is a result of confounding. Therefore, a role of habitual caffeine intake on cognitive function remains to be elucidated.

The most prominent findings of the current study were the inverse associations between tea (black or green) consumption and performance on all cognitive tests. These strong associations were also reflected in associations reported for our proxy measure of caffeine intake (derived from coffee and tea) and cognitive performance. To our knowledge there is no biological explanation for impaired cognitive function with tea intake. Rather, experimental data suggest the opposite (26, 27). Caffeine as well as other bioactives unique to tea such as catechins and L-theanine have all demonstrated psychostimulant effects and neuroprotective properties (28–30). In the UK Biobank, key socioeconomic factors implicated

TABLE 5 Associations between regular coffee consumption and cognitive function tests in the UK Biobank stratified by CMS_G[1]

Cups/day	0–1		1–2		3–4	
	β (95% CI)	*P*	*β* (95% CI)	*P*	*β* (95% CI)	*P*
Fluid Intelligence[2]						
0	Reference		Reference		Reference	
<1	0.11 (0.02, 0.19)	0.01	0.21 (0.13, 0.28)	<0.0001	0.19 (0.08, 0.30)	0.001
1	−0.004 (−0.06, 0.05)	0.89	0.01 (−0.04, 0.06)	0.81	−0.002 (−0.08, 0.07)	0.96
2–3	−0.01 (−0.06, 0.04)	0.71	0.03 (−0.02, 0.07)	0.27	0.09 (0.02, 0.15)	0.008
4–5	0.03 (−0.04, 0.10)	0.42	0.03 (−0.03, 0.09)	0.39	0.12 (0.04, 0.20)	0.004
6–7	−0.04 (−0.17, 0.09)	0.53	−0.06 (−0.16, 0.04)	0.22	−0.05 (−0.18, 0.08)	0.44
≥8	−0.02 (−0.20, 0.17)	0.86	0.01 (−0.13, 0.15)	0.90	−0.10 (−0.28, 0.07)	0.24
Cups/day, linear trend	−0.005 (−0.02, 0.01)	0.42	−0.0005 (−0.01, 0.01)	0.92	0.002 (−0.01, 0.01)	0.79
Reaction Time[3]						
0	Reference		Reference		Reference	
<1	−1.09 (−3.76, 1.58)	0.42	−1.25 (−3.65, 1.15)	0.31	1.37 (−2.08, 4.83)	0.44
1	3.53 (1.72, 5.35)	0.0001	2.57 (0.99, 4.15)	0.001	2.42 (0.16, 4.68)	0.04
2–3	3.02 (1.40, 4.64)	0.0003	2.73 (1.34, 4.12)	0.0001	2.71 (0.77, 4.65)	0.006
4–5	3.73 (1.47, 6.00)	0.001	2.69 (0.85, 4.54)	0.004	3.07 (0.58, 5.56)	0.02
6–7	3.51 (−0.36, 7.38)	0.08	3.71 (0.69, 6.73)	0.02	5.62 (1.78, 9.47)	0.004
≥8	3.35 (−2.31, 9.01)	0.25	0.80 (−3.45, 5.05)	0.71	6.23 (0.99, 11.46)	0.02
Cups/day, linear trend	0.68 (0.32, 1.03)	0.0002	0.47 (0.19, 0.75)	0.001	0.77 (0.40, 1.15)	<0.0001
Pairs Matching[3]						
0	Reference		Reference		Reference	
<1	0.012 (−0.004, 0.029)	0.15	−0.010 (−0.025, 0.005)	0.18	0.005 (−0.017, 0.026)	0.67
1	0.019 (0.008, 0.031)	0.001	0.019 (0.010, 0.029)	<0.0001	0.018 (0.004, 0.032)	0.01
2–3	0.015 (0.005, 0.025)	0.003	0.025 (0.016, 0.033)	<0.0001	0.019 (0.007, 0.031)	0.002
4–5	0.012 (−0.002, 0.026)	0.09	0.011 (−0.001, 0.022)	0.06	0.010 (−0.005, 0.025)	0.20
6–7	−0.008 (−0.032, 0.016)	0.49	0.011 (−0.007, 0.030)	0.24	0.007 (−0.017, 0.031)	0.55
≥8	−0.002 (−0.037, 0.033)	0.90	−0.008 (−0.034, 0.018)	0.53	0.039 (0.006, 0.071)	0.02
Cups/day, linear trend	0.001 (−0.001, 0.004)	0.19	0.002 (0.00001, 0.004)	0.05	0.003 (0.001, 0.005)	0.01
Symbol Digit Substitution[2]						
0	Reference		Reference		Reference	
<1	−0.27 (−0.50, −0.04)	0.02	−0.16 (−0.37, 0.05)	0.14	−0.18 (−0.49, 0.13)	0.26
1	−0.07 (−0.24, 0.09)	0.40	−0.17 (−0.31, −0.03)	0.02	−0.29 (−0.49, −0.09)	0.005
2–3	−0.22 (−0.37, −0.07)	0.003	−0.23 (−0.36, −0.11)	0.0002	−0.24 (−0.41, −0.06)	0.008
4–5	−0.03 (−0.24, 0.17)	0.74	−0.22 (−0.38, −0.05)	0.01	−0.27 (−0.49, −0.04)	0.02
6–7	−0.33 (−0.70, 0.04)	0.08	−0.33 (−0.61, −0.04)	0.02	−0.38 (−0.76, −0.01)	0.04
≥8	−1.02 (−1.60, −0.44)	0.001	−0.08 (−0.51, 0.34)	0.70	−0.94 (−1.47, −0.40)	0.001
Cups/day, linear trend	−0.05 (−0.09, −0.02)	0.002	−0.04 (−0.06, −0.01)	0.008	−0.07 (−0.10, −0.03)	0.0002
Trail A[3] (*P*-interaction = 0.03)						
0	Reference		Reference		Reference	
<1	−0.003 (−0.020, 0.013)	0.70	0.012 (−0.003, 0.026)	0.13	−0.003 (−0.025, 0.020)	0.81
1	0.001 (−0.010, 0.013)	0.83	0.006 (−0.004, 0.016)	0.26	0.009 (−0.006, 0.023)	0.26
2–3	0.004 (−0.007, 0.014)	0.48	0.003 (−0.006, 0.012)	0.52	0.009 (−0.004, 0.022)	0.18
4–5	−0.007 (−0.022, 0.008)	0.36	0.015 (0.003, 0.027)	0.01	0.012 (−0.004, 0.028)	0.15
6–7	0.002 (−0.024, 0.029)	0.86	0.015 (−0.005, 0.036)	0.14	0.031 (0.004, 0.058)	0.02
≥8	0.009 (−0.032, 0.050)	0.68	0.006 (−0.023, 0.036)	0.67	0.058 (0.020, 0.096)	0.003
Cups/day, linear trend	−0.0002 (−0.003, 0.002)	0.86	0.002 (0.00008, 0.004)	0.04	0.004 (0.001, 0.006)	0.003
Trail B[3] (*P*-interaction = 0.02)						
0	Reference		Reference		Reference	
<1	0.002 (−0.014, 0.018)	0.84	0.011 (−0.004, 0.025)	0.16	−0.018 (−0.040, 0.004)	0.11
1	0.008 (−0.003, 0.020)	0.15	0.012 (0.002, 0.022)	0.02	0.014 (−0.001, 0.028)	0.06
2–3	0.014 (0.004, 0.025)	0.006	0.011 (0.002, 0.019)	0.02	0.011 (−0.001, 0.024)	0.07
4–5	−0.004 (−0.019, 0.010)	0.56	0.018 (0.006, 0.029)	0.003	0.004 (−0.012, 0.019)	0.64
6–7	−0.005 (−0.031, 0.021)	0.70	0.007 (−0.013, 0.027)	0.50	0.032 (0.006, 0.058)	0.01
≥8	0.039 (−0.002, 0.080)	0.06	0.019 (−0.010, 0.049)	0.20	0.069 (0.032, 0.106)	0.0002
Cups/day, linear trend	0.001 (−0.001, 0.004)	0.32	0.002 (0.0004, 0.004)	0.02	0.004 (0.002, 0.007)	0.001
Prospective Memory Test[2]						
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
0	Reference		Reference		Reference	
<1	1.15 (1.02, 1.30)	0.03	1.37 (1.22, 1.54)	<0.0001	1.28 (1.09, 1.51)	0.003

(*Continued*)

TABLE 5 (*Continued*)

Cups/day	0–1		1–2		3–4	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
1	0.99 (0.92, 1.08)	0.85	1.03 (0.96, 1.10)	0.47	1.04 (0.94, 1.15)	0.48
2–3	0.99 (0.92, 1.07)	0.85	0.97 (0.91, 1.03)	0.29	1.01 (0.92, 1.11)	0.81
4–5	0.93 (0.84, 1.04)	0.20	1.02 (0.94, 1.11)	0.64	1.02 (0.91, 1.14)	0.77
6–7	0.96 (0.80, 1.14)	0.64	1.02 (0.89, 1.18)	0.74	1.00 (0.83, 1.20)	0.97
$\geq$8	0.99 (0.77, 1.27)	0.91	1.02 (0.84, 1.24)	0.86	0.79 (0.63, 1.00)	0.05
Cups/day, linear trend	0.99 (0.97, 1.01)	0.20	1.00 (0.98, 1.01)	0.62	0.99 (0.97, 1.01)	0.15

[1]Results from linear/logistic regressions adjusted for age, sex, smoking, Townsend deprivation index, education, income, employment status, home ownership, self-reported health, waist-to-hip ratio, physical activity, fasting time and intakes of alcohol, water, fish, red meat, fruit, vegetables, and tea (model 3). CMS_G: caffeine metabolism score; derived by summing the number of single-nucleotide polymorphism alleles multiplied by their β-coefficients and recalibrated such that it ranged from 0 to 4, with higher scores predicting faster caffeine metabolism.

[2]Positive β-coefficients for FI (difference in 13-point score) and SDS (difference in number of correct substitutions) and OR >1 for PM (correct on first attempt) correspond to higher performance compared with nondrinkers (0 cups/day).

[3]Negative β-coefficients for Pairs [difference in (log-transformed) number of errors], RT (difference in time, seconds, to respond), Trails A and Trails B [difference in (log transformed) time to complete] correspond to higher performance compared with nondrinkers (0 cups/d).

FI, fluid intelligence; Pairs, Pairs Matching; PM, prospective memory; RT, reaction time; SDS, symbol digit substitution.

in cognitive function were more closely correlated with tea drinking than coffee drinking. Despite adjustment for these and a comprehensive set of other confounders we cannot discount the possibility for residual confounding or, more likely, other unmeasured confounding factors. In our opinion, tea consumption may actually represent a novel marker of socioeconomic status in the UK Biobank not captured by other data collected and may be useful in future epidemiological analysis of this cohort.

In a systematic review of cross-sectional studies, habitual coffee, tea, and caffeine intake generally associated with better cognitive performance and lower prevalence of cognitive impairment (12). No study reported findings consistent with our current analysis. The largest among these studies involved the 1984–1985 Health and Lifestyle Survey of 9003 British adults which reported a dose-response improvement in all cognitive function tests with total coffee consumption (31). Higher tea consumption was initially associated with poor performance on all tasks but in fully adjusted models was not associated with performance. With further adjustment for coffee intake, tea intake was significantly associated with improved RT and visuospatial reasoning. In the current analysis of the UK Biobank, any evidence for improved cognitive performance with regular coffee intake was largely abolished or reversed after accounting for confounders and tea consumption. The latter was particularly influential and may suggest the initial benefits of coffee observed were just a consequence of not drinking tea. The diet assessment tool used in the previously mentioned British study did not distinguish between regular and decaffeinated coffee; the latter tended to benefit cognitive function in the UK Biobank.

In addition to unmeasured confounding, other limitations of the study should also be considered when interpreting the results of our analysis. The UK Biobank aimed to optimize the accuracy and completeness of data collected with maximal efficiency. As a result, few precise tests were administered for different cognitive function domains and thus measurement error may be of concern as well as an incomplete representation of cognition. The lack of information collected at the center on consumption of other beverages is also a limitation. For this reason, we did not conduct further stratified analysis such as the impact of coffee on cognition among nontea consumers since the latter may have been consuming a disproportionate amount of other beverages that may have also biased analysis. Finally, the UK Biobank is not representative of the sampling population, with evidence of a "healthy volunteer" selection bias (32) and thus extrapolation of our findings to a more general population is limited. Our currently analysis focused on whites. Race-specific studies are warranted in light of strong ties between culture and drinking behavior.

Our efforts to integrate genetic information as an efficient means to address some of the limitations of traditional nutritional epidemiology were not met with success. It is possible that confounding overwhelmed the relatively weaker genetic markers of caffeine metabolism. Biomarkers or other more objective measures of coffee and tea intake and cognition may be necessary to fully elucidate the role these beverages play in cognition, particularly in populations where drinking behaviors align closely with determinants of cognition. The potential for confounding we observed in analysis of cognitive function may not necessarily extend to *cognitive decline*; which, with mixed modeling approaches, can often account for confounding as well as for heterogeneous subgroups with different rates of both initial ability and decline. Studies of incident cognitive disorders, however, may still be subject to confounding. Meta-analyses suggest a J-shaped or nondose-response relation between habitual coffee intake and incident cognitive disorders (33, 34) and an inverse relation between tea and certain cognitive disorders (35, 36). Interestingly, none of these meta-analyses included UK populations.

In summary, the current analysis provides little support for a benefit of habitual caffeinated coffee or tea or caffeine intake on cognitive function. Residual and unmeasured confounding likely explain the unexpected inverse relations between these beverages and measures of cognitive function in the UK Biobank. A role of habitual caffeine intake on cognitive function therefore remains to be elucidated.

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The authors' contributions were as follows—MCC: was responsible for the current study concept, design and analysis, and also wrote the manuscript. MCC, SW, and MCM critically revised for important intellectual content and read and approved the final manuscript.

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