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Association of Coffee Drinking With Mortality by Genetic Variation in Caffeine Metabolism
Findings From the UK Biobank

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IMPORTANCE Prospective cohorts in North America, Europe, and Asia show consistent inverse associations between coffee drinking and mortality, including deaths from cardiovascular disease and some cancers. However, concerns about coffee, particularly among people with common genetic polymorphisms affecting caffeine metabolism and among those drinking more than 5 cups per day, remain.

OBJECTIVE To evaluate associations of coffee drinking with mortality by genetic caffeine metabolism score.

DESIGN, SETTING, AND PARTICIPANTS The UK Biobank is a population-based study that invited approximately 9.2 million individuals from across the United Kingdom to participate. We used baseline demographic, lifestyle, and genetic data form the UK Biobank cohort, with follow-up beginning in 2006 and ending in 2016, to estimate hazard ratios (HRs) for coffee intake and mortality, using multivariable-adjusted Cox proportional hazards models. We investigated potential effect modification by caffeine metabolism, defined by a genetic score of previously identified polymorphisms in *AHR, CYP1A2, CYP2A6,* and *POR* that have an effect on caffeine metabolism. Of the 502 641 participants who consented with baseline data, we included those who were not pregnant and had complete data on coffee intake and smoking status (n = 498 134).

EXPOSURES Total, ground, instant, and decaffeinated coffee intake.

MAIN OUTCOMES AND MEASURES All-cause and cause-specific mortality.

RESULTS The mean age of the participants was 57 years (range, 38-73 years); 271 019 (54%) were female, and 387 494 (78%) were coffee drinkers. Over 10 years of follow-up, 14 225 deaths occurred. Coffee drinking was inversely associated with all-cause mortality. Using non–coffee drinkers as the reference group, HRs for drinking less than 1, 1, 2 to 3, 4 to 5, 6 to 7, and 8 or more cups per day were 0.94 (95% CI, 0.88-1.01), 0.92 (95% CI, 0.87-0.97), 0.88 (95% CI, 0.84-0.93), 0.88 (95% CI, 0.83-0.93), 0.84 (95% CI, 0.77-0.92), and 0.86 (95% CI, 0.77-0.95), respectively. Similar associations were observed for instant, ground, and decaffeinated coffee, across common causes of death, and regardless of genetic caffeine metabolism score. For example, the HRs for 6 or more cups per day ranged from 0.70 (95% CI, 0.53-0.94) to 0.92 (95% CI, 0.78-1.10), with no evidence of effect modification across strata of caffeine metabolism score (P = .17 for heterogeneity).

CONCLUSIONS AND RELEVANCE Coffee drinking was inversely associated with mortality, including among those drinking 8 or more cups per day and those with genetic polymorphisms indicating slower or faster caffeine metabolism. These findings suggest the importance of noncaffeine constituents in the coffee-mortality association and provide further reassurance that coffee drinking can be a part of a healthy diet.

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Supplemental content

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Coffee is one of the most commonly consumed beverages worldwide. Epidemiologic studies have generally reported inverse associations with chronic disease, including cardiovascular disease[1,2]; diabetes[3]; Parkinson disease[4]; and liver,[5] colorectal,[6] and endometrial[7] cancer. Furthermore, prospective studies have consistently observed inverse associations with all-cause and cause-specific mortality.[8-16] Such evidence played a major role in the 2015 US Dietary Guidelines Advisory Committee report, which concluded that moderate coffee consumption of up to 5 eight-ounce cups per day can be a part of a healthy diet.[17]

Nevertheless, there remain concerns about the effects of coffee drinking. Coffee is a major source of caffeine, and between-person variation in caffeine metabolism is considerable. Clinical and epidemiologic studies have identified genetic variants that affect caffeine metabolism and coffee consumption,[18] and several studies have suggested that coffee drinkers with common genetic polymorphisms affecting caffeine metabolism may be at increased risk of cardiovascular disease.[19,20] However, the impact of common genetic polymorphisms that affect caffeine metabolism on the coffee-mortality association is unknown. There is also concern about heavy coffee drinking (≥6 cups/d) more generally. However, prior studies have had a limited number of participants in this intake range, precluding stable risk estimates.

We used the 500 000-participant UK Biobank cohort to investigate possible effect modification by caffeine metabolism score, defined by previously identified polymorphisms that affect caffeine metabolism.[18]

Key Points

Question Moderate coffee consumption has been inversely associated with mortality; however, does heavy intake, particularly among those with common genetic polymorphisms that impair caffeine metabolism, increase risk of mortality?

Findings This large prospective cohort study of a half million people found inverse associations for coffee drinking with mortality, including among participants drinking 1 up to 8 or more cups per day. No differences were observed in analyses that were stratified by genetic polymorphisms affecting caffeine metabolism.

Meaning This study provides further evidence that coffee drinking can be part of a healthy diet and offers reassurance to coffee drinkers.

Methods

Study Design

The UK Biobank study design has been described elsewhere.[21,22] In brief, the study mailed invitations to approximately 9.2 million individuals in the United Kingdom's National Health Service (NHS), ages 40 to 69 years who resided within 40 km of 22 assessment centers across the United Kingdom.[21] In total, 503 317 individuals visited assessment centers between 2006 and 2010[22]; answered comprehensive touchscreen questionnaires, including about diet; received physical examinations; and provided biological samples. Data from 502 641 participants were available for our study. We excluded participants with incomplete data on coffee intake (n = 2269) or smoking status (n = 1866), women who were pregnant or unsure whether they were pregnant (n = 369), and those with no follow-up time (n = 3), resulting in an analytic cohort of 498 134 participants.

The UK Biobank study was approved by the National Information Governance Board for Health and Social Care and the NHS North West Multicenter Research Ethics Committee. Written consent was obtained from all participants. According to the UK Biobank information leaflet for participants, participation is "entirely voluntary" and participants are "free to withdraw at any time later."[21,22]

Cohort Follow-up

Follow-up time was counted from the date of assessment center visit until the date of death or the date of censor (ie, January 31, 2016, for England and Wales and November 30, 2015, for Scotland), whichever came first. For cause-specific mortality analyses, individuals who died from other causes were censored at their date of death.

Death Ascertainment

Vital status, date, and underlying (primary) cause of death were provided by the National Health Service (NHS) Information Centre for participants from England and Wales and by the NHS Central Register, Scotland, for those from Scotland. We defined the following 3 broad categories (ie, causes with >500 deaths) of cause-specific mortality using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10),* codes: cancer (C00-D48), cardiovascular disease (I00-I79), and respiratory diseases (J09-J18 and J40-J47). In addition, for cancer and cardiovascular disease, we further defined the common causes of death (ie, causes with >500 deaths) within these broad categories: colorectal cancer (C18-C20), bronchus and lung cancer (C34), female breast cancer (C50), and pancreatic cancer (C25); ischemic heart diseases (I20-I25); and stroke (I60-I69).

Exposure Assessment

Participants were asked "How many cups of coffee do you drink each day (including decaffeinated coffee)?" Participants selected either the number of cups, "Less than 1," "Do not know," or "Prefer not to answer." If participants reported drinking more than 10 cups, they were asked to confirm the response. For the main analysis of coffee and all-cause mortality, we defined coffee intake as follows: 0, less than 1, 1, 2 to 3, 4 to 5, 6 to 7, and 8 or more cups per day. The top 2 categories were collapsed for secondary analyses, to preserve sample size. Coffee drinkers were also asked "What type of coffee do you usually drink?" and were able to select 1 of 6 mutually exclusive responses including "decaffeinated coffee (any type)," "instant coffee," or "ground coffee (include espresso, filter, etc)."

The baseline questionnaire also assessed potential confounding factors, including smoking, alcohol, tea, race, education, physical activity, and body mass index (BMI) (calcu-

lated as weight in kilograms divided by height in meters squared). We created a 25-level detailed smoking variable by combining data on smoking status, lifetime smoking, previous smoking intensity, current smoking intensity, time since quitting for former smokers, type of tobacco smoked previously, and type of tobacco smoked currently. We created a 6-level variable for alcohol drinking by combining data on drinking status and amount consumed. Less than 9% of the cohort lacked data on any single covariate, and indicator variables were created to represent missing data categories in regression models.

All UK Biobank participants were genotyped using genome-wide arrays. The initial 50 000 participants were genotyped using the Affymetrix UK BiLEVE Axiom array, while the remaining were genotyped using the Affymetrix UK Biobank Axiom array. The 2 arrays were extremely similar and can be imputed together. Quality control and imputation to the Haplotype Reference Consortium (HRC), version 1.1, and UK10K reference panels was performed centrally by the Wellcome Trust Centre for Human Genetics as described elsewhere.[23] Genetic data were available from 403 816 participants in our analytic sample after excluding sample outliers based on heterozygosity and 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 2 genetic "caffeine metabolism" scores (CMS_G) by adding the number of alleles of single base changes, or single-nucleotide polymorphisms (SNPs), previously associated with blood caffeine metabolite levels, and the map near genes with plausible roles in caffeine metabolism.[24] All SNPs were available from the HRC, version 1.1, imputation. CMS_{G2} included the 2 SNPs presenting with the largest effect sizes in a genome-wide association study (GWAS) of caffeine metabolites[24]: rs2472297 (near *CYP1A2*) and rs6968554 (near *AHR*). CMS_{G4} also included rs17685 (in *POR*) and rs56113850 (near *CYP2A6*). Corresponding weighted genetic "caffeine metabolism" scores ($wCMS_G$) were derived 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[24] and p is the SNP minor allele frequency. Estimated β-coefficients for rs6968554, rs2472297, rs17685, and rs56113850 were 17.58, 21.58, 3.79, and 19.43, respectively. Weighted scores were then calibrated such that both CMS_{G2} and $wCMS_{G2}$ ranged from 0 to 4 and both CMS_{G4} and $wCMS_{G4}$ ranged from 0 to 8, with higher scores predicting faster caffeine metabolism. All 4 SNPs have previously been linked to coffee consumption in the UK Biobank.[24,25] Because rs762551 (*CYP1A2*1F*) has been examined previously for interactions with coffee and disease outcomes,[19] we conducted a separate analysis of this SNP.`

Statistical Analysis

We used Cox proportional hazard regression models to estimate hazard ratios (HRs) and 95% CIs for mortality. Person-years (ie, calendar time) of follow-up was used as the underlying time metric. We estimated the Spearman partial correlation coefficients between coffee intake and each CMS_G, adjusting for age, sex, smoking status, genotyping array, and the first 5 genetic principal components. We tested the proportional-hazards assumption by comparing the multivariable model with the interaction term between person-time and coffee intake to the model without it; we observed no deviations from this assumption. Statistical tests were 2-sided, and $P < .05$ was interpreted as statistically significant. We used SAS software (version 9.4; SAS Institute Inc) and the computational resources of the National Institutes of Health's (NIH) High-Performance Computing Biowulf cluster to conduct analyses.

In our analysis of coffee intake with all-cause mortality, we first adjusted for age and sex, followed by additional adjustment for other potential confounders; adjustment for detailed smoking history had the largest effect on risk estimates. We tested for trends across increasing categories of coffee intake by modeling the midpoint of each intake category as a continuous variable, with the highest intake categories of 8 or more cups per day and 6 or more cups per day assigned values of 8 and 6, respectively. We evaluated the multivariable-adjusted associations of coffee intake with cause-specific mortality and with all-cause mortality by coffee type, including non-coffee drinkers as the reference group in each subgroup analysis. We also ran multivariable-adjusted models stratified by the following potential effect modifiers: $wCMS_{G2}$ (0-1, >1 to 2, or >2), CMS_{G4} (0-2, >2 to 3, >3 to 4, or >4), age (<55 or ≥55 years), sex (male or female), smoking status (never, former, or current smoker), general health status (excellent/good or fair/poor health), BMI (18.5 to <25.0, 25.0 to <30.0, or ≥30.0), history of diabetes (yes or no), and history of cancer, heart attack, or stroke (yes or no). The thresholds for strata of CMS_G were based on the distribution of the scores; however, we also considered a 1-unit and 2-unit increase in the weighted scores (eTable 1 in the Supplement). We assessed potential effect modification by modeling the cross-product term of the stratifying variable with coffee intake; the P value for heterogeneity corresponds to the likelihood ratio test comparing the multivariable models with and without the cross-product terms for each level of the stratifying variable with coffee intake (continuous) except in the case of genetic caffeine metabolism scores, which were modeled as continuous variables. Finally, to better understand the potential effect of reverse causality, we conducted a lag analysis in which we examined deaths occurring in 0 to less than 3 years, 3 to less than 5 years, and 5 or more years of follow-up.

Results

In the UK Biobank cohort, 110 640 (22%) participants were non-coffee drinkers. Among coffee drinkers, 214 119 (56%), 87 665 (23%), and 74 053 (19%) reported usually drinking instant, ground, and decaffeinated coffee, respectively. Coffee drinkers, compared with non-coffee drinkers, were more likely to be male, white, former smokers, and drink alcohol. Participants drinking 4 or more cups per day, compared with those drinking less coffee and nondrinkers, were more likely to drink instant coffee and be current smokers, whereas participants

drinking 1 to 3 cups per day were older, more likely to have a university degree, and more likely to report "excellent" health (**Table 1**).

Over 10 years of follow-up (median, 7 years) and 3.4 million person-years, 14 225 deaths occurred. After multivariable adjustment, we observed an inverse dose-dependent association ($P < .001$ for trend) for total coffee intake and all-cause mortality (**Table 2**). The HRs for drinking less than 1, 1, 2 to 3, 4 to 5, 6 to 7, and 8 or more cups per day were 0.94 (95% CI, 0.88-1.01), 0.92 (95% CI, 0.87-0.97), 0.88 (95% CI, 0.84-0.93), 0.88 (95% CI, 0.83-0.93), 0.84 (95% CI, 0.77-0.92), and 0.86 (95% CI, 0.77-0.95), respectively. Approximately 8294 (58%), 2833 (20%), and 553 (4%) deaths in the cohort were due to cancer, cardiovascular disease, and respiratory disease, respectively. We observed inverse associations for coffee drinking with all-cancer and all-cardiovascular disease mortality. The number of deaths for specific types of cancer and cardiovascular disease were modest, yet we did observe potential inverse associations, without statistical significance, for stroke, colorectal cancer, and female breast cancer. We observed inverse associations for each coffee type with all-cause and cause-specific mortality; associations were generally stronger for ground coffee than for instant or decaffeinated coffee (**Table 3**).

Next, we evaluated the effect of CMS_G, defined using 2 or 4 known caffeine-related SNPs. Each score was positively and statistically significantly correlated with coffee intake, with Spearman partial correlation coefficients of 0.07 ($P < .001$) for both CMS_{G2} and CMS_{G4}, reflecting prior UK Biobank reports.[24,25] Using the weighted CMS_{G2}, based on variants in *AHR* and *CYP1A2*, participants with a lower $wCMS_{G2}$ or $wCMS_{G4}$ (ie, slower caffeine metabolizers) had similar associations for coffee drinking and mortality as participants with a higher $wCMS_{G2}$ ($P = .75$ for heterogeneity) or $wCMS_{G4}$ ($P = .17$ for heterogeneity) (ie, faster caffeine metabolizers), indicating no modification of the association between coffee drinking and all-cause mortality by these common polymorphisms related to caffeine metabolism (**Table 4**). We found similar results when limiting the CMS_G analyses to those with white and/or British ancestry only (data not shown), using different thresholds (ie, 1- or 2-unit increase) for $wCMS_G$ strata (eTable 1 in the Supplement), stratifying by *CYP1A2*1F* only (eTable 2 in the Supplement), and using the unweighted CMS_G (eTable 3 in the Supplement). In addition, we observed a positive association between $wCMS_{G4}$ and all-cause mortality in multivariable models with (HR for a 1-unit increase in $wCMS_{G4}$ = 1.02; 95% CI, 1.01-1.03) and without (HR for a 1-unit increase in $wCMS_{G4}$ = 1.02; 95% CI, 1.00-1.03) adjustment for coffee and tea intake.

Associations for coffee drinking and mortality did not meaningfully differ by sex, age group, BMI, history of diabetes, or previous diagnosis of cancer, heart attack, or stroke. We did observe a statistically significant interaction between coffee drinking and self-reported health, with a stronger inverse association among those reporting worse health than those reporting better health (**Table 5**). Associations also seemed stronger among former and current smokers than never-smokers, with the latter association lacking statistical significance. However, the formal test for interaction was not statistically significant. Finally, inverse associations seemed stronger for deaths occurring within the first 3 years of follow-up, although similar patterns were also observed in later years (eTable 4 in the Supplement).

Discussion

In this large study of nearly 500 000 people in the United Kingdom, coffee drinking was inversely associated with all-cause mortality, with statistically significant inverse associations observed in participants drinking 1 to 8 or more cups per day. Inverse associations were also observed for ground and instant coffee, although were somewhat weaker for instant coffee, and for cancer and cardiovascular disease mortality, the 2 most common causes of death in the cohort. Common genetic polymorphisms predisposing individuals to slower or faster caffeine metabolism did not modify associations between coffee drinking and mortality, although, as previously reported in the UK Biobank,[24,25] higher CMS_G was significantly correlated with higher coffee intake. We also observed inverse associations for both caffeinated and decaffeinated coffee, further suggesting the importance of noncaffeine compounds in the association.

Our findings are consistent with prior, large, prospective investigations of coffee drinking and all-cause mortality conducted in the United States,[9,11-13] Europe,[10] and Asia,[15] as well as the most recent meta-analyses[14,16] and the 2015 US Dietary Guidelines Advisory Committee report, which concluded that moderate coffee consumption can be a part of a healthy diet.[17] However, it should be noted that none of these prior studies were able to look at potential effect modification by caffeine metabolism. In addition, our findings for all-cancer and all-cardiovascular disease mortality are reflective of recent large prospective studies of certain cancers[8] and cardiovascular disease.[13]

There has been concern about the health effects of heavy coffee drinking, particularly in participants with common genetic polymorphisms that affect caffeine metabolism. For example, prior studies have suggested that variants in *CYP1A2*, encoding the enzyme responsible for more than 95% of caffeine metabolism, may alter associations of coffee drinking with cardiovascular-related outcomes, with slower caffeine metabolizers having higher risk of developing hypertension[20] or having a myocardial infarction[19] relative to their nondrinking counterparts, whereas faster caffeine metabolizers who drink coffee are at no or lower risk of these outcomes. However, prior large prospective cohorts have lacked genetic data on most participants, such that it was not possible to examine how genetic variation in caffeine metabolism affects associations between coffee drinking and mortality. With genetic data on more than 400 000 participants in the UK Biobank, we were able to stratify each participant based on their genetic susceptibility for slower or faster caffeine metabolism. We found very similar associations between coffee drinking and mortality across levels of examined caffeine metabolism scores. Genetic caffeine metabolism scores are also associated with coffee and dietary caffeine intake behavior[18,24,25] and have therefore been

Table 1. Baseline Characteristics by Total Coffee Intake in the UK Biobank Cohort[a]

Characteristic	Coffee Consumption, Cups/d, by 498 134 Participants, No. (%)						
	0	<1	1	2-3	4-5	6-7	≥8
No. (%)	110 640 (22.2)	36 159 (7.3)	99 895 (20.1)	154 337 (31.0)	66 539 (13.4)	20 539 (4.1)	10 025 (2.0)
Age, median (IQR), y	56 (49-62)	57 (50-63)	59 (51-64)	59 (51-64)	58 (50-63)	57 (50-63)	55 (48-61)
Tea intake, median (IQR), cups/d	4 (2-6)	4 (3-6)	4 (2-5)	3 (1-4)	2 (0-3)	0.5 (0-3)	0 (0-2)
$wCMS_{G2}$, median (IQR)[b]	1.8 (0.9-2.0)	1.8 (0.9-2.0)	1.8 (0.9-2.0)	1.8 (0.9-2.0)	1.8 (0.9-2.0)	1.8 (0.9-2.9)	1.8 (0.9-2.9)
$wCMS_{G4}$, median (IQR)[b]	3.6 (2.5-4.7)	3.6 (2.5-4.7)	3.7 (2.5-4.9)	3.7 (2.6-4.9)	3.8 (2.6-5.0)	3.9 (2.6-5.0)	3.9 (2.7-5.0)
rs762551 (*CYP1A2*1A*)[b]							
0	7825 (8.8)	2510 (8.6)	6557 (8.1)	9566 (7.6)	3848 (7.1)	1140 (6.9)	507 (6.3)
1	36 447 (41.0)	11 925 (40.16)	33 065 (40.7)	50 271 (39.9)	21 050 (39.1)	6435 (38.8)	3075 (38.3)
2	44 601 (50.2)	14 917 (50.8)	41 620 (51.2)	66 017 (52.5)	28 978 (53.8)	9024 (54.4)	4438 (55.3)
Coffee type[c]							
Instant	NA	17 296 (51.0)	50 855 (52.9)	83 929 (55.7)	41 490 (63.7)	13 623 (67.7)	6926 (71.2)
Ground	NA	9736 (28.7)	25 832 (26.9)	38 133 (25.3)	10 606 (16.3)	2336 (11.6)	1022 (10.5)
Decaffeinated	NA	6854 (20.2)	19 487 (20.3)	28 725 (19.1)	13 044 (20.0)	4160 (20.7)	1783 (18.3)
Sex							
Male	46 233 (41.8)	16 179 (44.7)	42 824 (42.9)	71 855 (46.6)	33 704 (50.7)	10 573 (51.5)	5747 (57.3)
Female	64 407 (58.2)	19 980 (55.3)	57 071 (57.1)	82 482 (53.4)	32 835 (49.3)	9966 (48.5)	4278 (42.7)
Smoking status							
Never	65 025 (58.8)	21 127 (58.4)	57 666 (57.7)	84 410 (54.7)	32 567 (48.9)	8619 (42.0)	3301 (32.9)
Former	34 767 (31.4)	12 045 (33.3)	34 877 (34.9)	55 591 (36.0)	24 572 (36.9)	7531 (36.7)	3333 (33.2)
Current	10 848 (9.8)	2987 (8.3)	7352 (7.4)	14 336 (9.3)	9400 (14.1)	4389 (21.4)	3391 (33.8)
Race/ethnicity							
White	99 427 (90.2)	33 548 (93.1)	93 754 (94.1)	148 527 (96.6)	64 898 (97.9)	20 113 (98.3)	9793 (98.0)
Black	3419 (3.1)	757 (2.1)	1720 (1.7)	1472 (1.0)	393 (0.6)	86 (0.4)	43 (0.4)
Asian	5155 (4.7)	1102 (3.1)	2464 (2.5)	1851 (1.2)	397 (0.6)	94 (0.5)	32 (0.3)
Mixed	782 (0.7)	250 (0.7)	638 (0.6)	826 (0.5)	303 (0.5)	72 (0.4)	60 (0.6)
Other	1451 (1.3)	374 (1.0)	1007 (1.0)	1154 (0.8)	310 (0.5)	105 (0.5)	61 (0.6)
Self-reported health							
Excellent	15 804 (14.4)	5745 (16.0)	16 945 (17.0)	27 649 (18.0)	11 061 (16.7)	2965 (14.5)	1350 (13.6)
Good	61 050 (55.5)	21 036 (58.5)	58 767 (59.1)	91 471 (59.5)	38 576 (58.2)	11 470 (56.1)	5052 (50.7)
Fair	26 253 (23.9)	7483 (20.8)	19 859 (20.0)	29 334 (19.1)	13 945 (21.0)	4892 (23.9)	2653 (26.6)
Poor	6859 (6.2)	1683 (4.7)	3912 (3.9)	5323 (3.5)	2677 (4.0)	1115 (5.5)	900 (9.0)

(continued)

Table 1. Baseline Characteristics by Total Coffee Intake in the UK Biobank Cohort[a] (continued)

Characteristic	Coffee Consumption, Cups/d, by 498 134 Participants, No. (%)						
	0	<1	1	2-3	4-5	6-7	≥8
BMI							
<18.5	628 (0.6)	197 (0.6)	482 (0.5)	651 (0.4)	255 (0.4)	88 (0.4)	61 (0.6)
18.5 to <25.0	35 035 (32.3)	12 330 (34.7)	34 761 (35.4)	49 339 (32.5)	17 666 (27.0)	5091 (25.2)	2563 (26.1)
25.0 to <30.0	44 542 (41.1)	14 865 (41.9)	41 338 (42.2)	66 265 (43.7)	29 246 (44.7)	8751 (43.4)	4100 (41.8)
30.0 to <35.0	19 597 (18.1)	5845 (16.5)	15 520 (15.8)	26 015 (17.2)	13 109 (20.0)	4365 (21.6)	2137 (21.8)
≥35.0	8517 (7.9)	2259 (6.4)	5965 (6.1)	9398 (6.2)	5113 (7.8)	1877 (9.3)	948 (9.7)
Physical activity (>10 min of moderate or vigorous activity), d/wk							
0	13 227 (13.3)	3651 (11.1)	9244 (10.0)	14 656 (10.2)	7403 (12.0)	2704 (14.4)	1516 (16.7)
1-2	13 330 (13.4)	4656 (14.2)	12 319 (13.3)	19 915 (13.9)	9096 (14.8)	2807 (15.0)	1220 (13.4)
2-3	16 665 (16.7)	6073 (18.5)	16 721 (18.1)	26 365 (18.4)	11 197 (18.2)	3193 (17.0)	1374 (15.1)
≥5	56 574 (56.7)	18 450 (56.2)	54 101 (58.6)	82 470 (57.5)	33 814 (55.0)	10 052 (53.6)	4991 (54.8)
Alcohol drinking status, drink/wk							
Never	9704 (8.8)	1487 (4.1)	3813 (3.8)	4307 (2.8)	1772 (2.7)	641 (3.1)	372 (3.7)
Former	6403 (5.8)	1031 (2.9)	2701 (2.7)	3898 (2.5)	2196 (3.3)	921 (4.5)	744 (7.4)
Current, <1	31 488 (28.5)	8958 (24.8)	22 138 (22.2)	29 188 (18.9)	13 388 (20.1)	4958 (24.2)	2883 (28.8)
Current, >1 to <7	24 656 (22.3)	9605 (26.6)	27 538 (27.6)	40 333 (26.2)	15 849 (23.8)	4350 (21.2)	1771 (17.7)
Current, 1 to 3	30 237 (27.4)	12 134 (33.6)	35 962 (36.0)	62 989 (40.8)	26 649 (40.1)	7603 (37.1)	3156 (31.5)
Current, >3	8028 (7.3)	2898 (8.0)	7668 (7.7)	13 490 (8.7)	6619 (10.0)	2040 (9.9)	1080 (10.8)
Education level							
College or university degree	29 355 (34.6)	12 440 (41.1)	33 169 (40.7)	55 367 (42.7)	21 949 (39.9)	5732 (34.9)	2524 (32.5)
A levels/AS levels or equivalent	11 471 (13.5)	4384 (14.5)	11 216 (13.8)	17 592 (13.6)	7212 (13.1)	2246 (13.7)	1015 (13.1)
O levels/GCSEs or equivalent	23 441 (27.7)	7784 (25.7)	20 795 (25.5)	31 999 (24.7)	14 060 (25.6)	4505 (27.4)	2138 (27.5)
CSEs or equivalent	7245 (8.5)	1663 (5.5)	4656 (5.7)	7347 (5.7)	3688 (6.7)	1353 (8.2)	761 (9.8)
NVQ or HND or HNC equivalent	7766 (9.2)	2224 (7.4)	6312 (7.7)	9215 (7.1)	4609 (8.4)	1535 (9.3)	830 (10.7)
Other professional qualifications	5495 (6.5)	1754 (5.8)	5301 (6.5)	8098 (6.2)	3460 (6.3)	1055 (6.4)	504 (6.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CSE, Certificate of Secondary Education; GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; IQR, interquartile range; NA, not applicable; NVQ, National Vocational Qualification; $wCMS_{G2}$, weighted genetic caffeine metabolism score defined using 2 single-nucleotide polymorphisms (near *AHR, CYP1A2*); $wCMS_{G4}$, weighted genetic caffeine metabolism score defined using 4 single-nucleotide polymorphisms (near *AHR, CYP1A2, POR, CYP2A6*).

[a] Numbers may not sum to n = 498 134 owing to missing data, and percentages may not total 100% owing to rounding.

[b] n = 403 816 included in the genetic analyses.

[c] n = 7086 reported "other type of coffee"; n = 4571 had missing data.

Table 2. Hazard Ratios for Coffee Intake and All-Cause and Cause-Specific Mortality in the UK Biobank

Cause of Death	Coffee Consumption, Cups/d, by 498 134 Participants, HR (95% CI)							
	0 (n = 110 640)	<1 (n = 36 159)	1 (n = 99 895)	2-3 (n = 154 337)	4-5 (n = 66 539)	6-7 (n = 20 539)	≥8 (n = 10 025)	*P* Value for Trend[a]
All Causes								
Deaths, No.	3395	994	2694	4098	1957	690	397	
Age- and sex-adjusted	1.00	0.83 (0.77-0.89)	0.77 (0.73-0.81)	0.76 (0.72-0.79)	0.87 (0.82-0.92)	1.01 (0.93-1.10)	1.30 (1.17-1.45)	.05
Multivariable-adjusted[b]	1.00	0.94 (0.88-1.01)	0.92 (0.87-0.97)	0.88 (0.84-0.93)	0.88 (0.83-0.93)	0.84 (0.77-0.92)	0.86 (0.77-0.95)	<.001
Cause of Death	**0 (n = 110 640)**	**<1 (n = 36 159)**	**1 (n = 99 895)**	**2-3 (n = 154 337)**	**4-5 (n = 66 539)**	**≥6 (n = 30 564)**		***P* Value for Trend**
All cancer								
Deaths, No.	1885	588	1628	2450	1149	594		
Multivariable-adjusted[b]	1 [Reference]	0.97 (0.88-1.06)	0.95 (0.89-1.02)	0.91 (0.86-0.97)	0.92 (0.85-1.00)	0.87 (0.79-0.96)		.003
Bronchial and Lung Cancer								
Deaths, No.	383	90	229	381	245	160		
Multivariable-adjusted[b]	1 [Reference]	0.84 (0.66-1.05)	0.79 (0.67-0.94)	0.80 (0.69-0.93)	0.91 (0.77-1.09)	0.86 (0.70-1.05)		.41
Colorectal Cancer								
Deaths, No.	169	61	156	256	90	57		
Multivariable-adjusted[b]	1 [Reference]	1.04 (0.77-1.39)	0.93 (0.74-1.16)	0.94 (0.77-1.15)	0.74 (0.56-0.97)	0.96 (0.70-1.32)		.14
Female Breast Cancer[c]								
Deaths, No.	193	58	145	221	73	33		
Multivariable-adjusted	1 [Reference]	0.93 (0.69-1.26)	0.84 (0.68-1.05)	0.91 (0.74-1.12)	0.75 (0.56-0.99)	0.74 (0.50-1.09)		.06
Pancreatic Cancer								
Deaths, No.	115	36	119	172	78	32		
Multivariable-adjusted[b]	1 [Reference]	0.94 (0.65-1.37)	1.05 (0.81-1.36)	0.96 (0.75-1.24)	0.99 (0.73-1.34)	0.81 (0.54-1.24)		.44
All Cardiovascular Disease								
Deaths, No.	676	196	524	781	417	239		
Multivariable-adjusted[b]	1 [Reference]	0.97 (0.82-1.13)	0.93 (0.83-1.05)	0.86 (0.77-0.96)	0.91 (0.80-1.04)	0.87 (0.74-1.02)		.05
Ischemic Heart Disease								
Deaths, No.	375	111	293	460	251	144		
Multivariable-adjusted[b]	1 [Reference]	1.00 (0.80-1.23)	0.97 (0.83-1.13)	0.94 (0.81-1.08)	0.99 (0.83-1.17)	0.91 (0.74-1.12)		.50
Stroke								
Deaths, No.	148	34	106	140	73	42		
Multivariable-adjusted[b]	1 [Reference]	0.76 (0.52-1.10)	0.83 (0.64-1.07)	0.70 (0.55-0.89)	0.75 (0.55-1.01)	0.75 (0.52-1.09)		.05
Respiratory Disease								
Deaths, No.	154	34	77	137	78	73		
Multivariable-adjusted[b]	1 [Reference]	0.88 (0.61-1.28)	0.74 (0.56-0.98)	0.88 (0.69-1.12)	0.92 (0.69-1.24)	1.20 (0.88-1.64)		.25

Abbreviations: CSE, Certificate of Secondary Education; GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; HR, hazard ratio; NVQ, National Vocational Qualification.

[a] *P* value for trend corresponds to the χ^2 test statistic for coffee intake as a continuous variable, using the midpoint of each category and values of 8 and 6 for the highest intake categories of ≥8 cups/d and ≥6 cups/d, respectively.

[b] Multivariable model is also adjusted for detailed smoking history (25-level variable incorporating current smoking status, smoking intensity [current and former smokers]; time since quitting [former smokers], and cigar and pipe use [current and former smokers]); race/ethnicity (white, black, Asian, mixed, or other race); alcohol drinking (never drinker, former drinker, infrequent drinker [<1 drink/wk], occasional drinker [>1 drink/wk but <1 drink/d], moderate daily drinker [1-3 drinks/d], or heavy daily drinker [>3 drinks/d]); general health status (excellent, good, fair, or poor); education level (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); and body mass index (calculated as weight in kilograms divided by height in meters squared) (<18.5, 18.5 to <25.0, 25.0 to <30.0, 30.0 to <35.0, or ≥35.0); physical activity (0, 1-2, 3-4, or ≥5 d of >10 min of moderate- or vigorous-intensity activity); tea intake (0, <1, 1, 2 or 3, 4 or 5, or ≥6 cups/d).

[c] n = 271 019 women.

Table 3. Multivariable-Adjusted Hazard Ratios (HRs) and 95% CIs for Coffee Intake and All-Cause and Cause-Specific Mortality by Coffee Type in the UK Biobank

Cause of Death	Coffee Consumption, Cups/d, by 498 134 Participants						*P* Value for Trend [a]
	0	<1	1	2-3	4-5	≥6	
Instant Coffee vs None (n = 324 759)[b]							
All causes							
Deaths, No.	3395	552	1484	2427	1277	779	<.001
HR (95% CI)[c]	1 [Reference]	0.98 (0.90-1.07)	0.90 (0.85-0.96)	0.90 (0.85-0.95)	0.87 (0.81-0.93)	0.85 (0.78-0.92)	
All cancer							
Deaths, No.	1885	315	875	1389	742	420	.004
HR (95% CI)[c]	1 [Reference]	0.99 (0.88-1.11)	0.92 (0.85-1.00)	0.89 (0.83-0.96)	0.91 (0.83-1.00)	0.87 (0.77-0.98)	
All CVD							
Deaths, No.	676	112	280	490	296	178	.47
HR (95% CI)[c]	1 [Reference]	0.98 (0.80-1.20)	0.86 (0.74-0.99)	0.90 (0.79-1.02)	0.97 (0.84-1.13)	0.91 (0.76-1.09)	
Ground Coffee vs None (n = 198 305)[b]							
All causes							
Deaths, No.	3395	205	596	812	248	92	<.001
HR (95% CI)[c]	1 [Reference]	0.89 (0.77-1.02)	0.94 (0.85-1.03)	0.80 (0.74-0.87)	0.76 (0.67-0.87)	0.74 (0.60-0.92)	
All cancer							
Deaths, No.	1885	132	385	537	153	48	.004
HR (95% CI)[c]	1 [Reference]	0.96 (0.80-1.15)	1.03 (0.91-1.15)	0.91 (0.82-1.02)	0.85 (0.71-1.01)	0.73 (0.55-0.98)	
All CVD							
Deaths, No.	676	40	127	129	32	17	<.001
HR (95% CI)[c]	1 [Reference]	0.90 (0.65-1.24)	1.01 (0.83-1.24)	0.63 (0.51-0.77)	0.46 (0.32-0.66)	0.61 (0.37-1.00)	
Decaffeinated Coffee vs None (n = 184 693)							
All causes							
Deaths, No.	3395	157	492	733	379	173	<.001
HR (95% CI)[c]	1 [Reference]	0.86 (0.73-1.01)	0.88 (0.80-0.97)	0.85 (0.78-0.93)	0.90 (0.81-1.01)	0.78 (0.66-0.91)	
All cancer							
Deaths, No.	1885	93	303	457	217	106	.09
HR (95% CI)[c]	1 [Reference]	0.87 (0.70-1.07)	0.93 (0.82-1.05)	0.92 (0.83-1.02)	0.93 (0.80-1.08)	0.88 (0.72-1.08)	
All CVD							
Deaths, No.	676	26	93	130	82	31	.03
HR (95% CI)[c]	1 [Reference]	0.78 (0.52-1.15)	0.88 (0.70-1.09)	0.78 (0.64-0.95)	0.96 (0.75-1.22)	0.67 (0.46-0.98)	

Abbreviations: CSE, Certificate of Secondary Education; CVD, cardiovascular disease; GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; NVQ, National Vocational Qualification.

[a] *P* value for trend corresponds to the χ^2 test statistic for coffee intake as a continuous variable, using the midpoint of each category and a value of 6 for ≥6 cups/d.

[b] Sample size for each coffee type includes n = 110 640 non–coffee drinkers; n = 11 657 participants were missing data on coffee type or reported "other type of coffee" to the question "What type of coffee do you usually drink?"

[c] Multivariable model is adjusted for age, sex, detailed smoking history (25-level variable incorporating current smoking status, smoking intensity [current and former smokers]; time since quitting [former smokers], and cigar and pipe use [current and former smokers]); race/ethnicity (white, black, Asian, mixed, or other race); alcohol drinking (never drinker, former drinker, infrequent drinker [<1 drink/wk], occasional drinker [>1 drink/wk but <1 drink/d], moderate daily drinker [1 to 3 drinks/d], or heavy daily drinker [>3 drinks/d]); general health status (excellent, good, fair, or poor); education level (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); and body mass index (calculated as weight in kilograms divided by height in meters squared) (<18.5, 18.5 to <25.0, 25.0 to <30.0, 30.0 to <35.0, or ≥35.0); physical activity (0, 1-2, 3-4, or ≥5 d of >10 minutes of moderate- or vigorous-intensity activity); tea intake (0, <1, 1, 2 or 3, 4 or 5, or ≥6 cups/d).

Table 4. Association Between Coffee Intake and All-Cause Mortality in the UK Biobank Stratified by Weighted Genetic Caffeine Metabolism Score ($wCMS_G$)[a]

	Coffee Consumption, Cups/d						*P* Value	
	0	<1	1	2-3	4-5	≥6	Trend[b]	Heterogeneity[c]
Overall (n = 403 816)								
Deaths, No.	2654	786	2141	3256	1546	867		
HR (95% CI)[d]	1 [Reference]	0.94 (0.87-1.02)	0.91 (0.86-0.97)	0.87 (0.83-0.92)	0.86 (0.80-0.92)	0.84 (0.77-0.91)	<.001	
CMS_{G2}[e]								
0 to 1 (n = 139 311)								
Deaths, No.	982	291	751	1031	511	257		
HR (95% CI)[d]	1 [Reference]	0.94 (0.82-1.07)	0.90 (0.81-0.99)	0.83 (0.76-0.91)	0.93 (0.83-1.05)	0.91 (0.79-1.05)	.11	
>1 to 2 (n = 178 336)								
Deaths, No.	1151	329	939	1468	669	371		.75
HR (95% CI)[d]	1 [Reference]	0.90 (0.80-1.02)	0.91 (0.83-0.99)	0.88 (0.81-0.96)	0.83 (0.75-0.92)	0.79 (0.69-0.89)	<.001	
>2 (n = 86 169)								
Deaths, No.	521	166	451	757	366	239		
HR (95% CI)[d]	1 [Reference]	1.05 (0.88-1.25)	0.96 (0.85-1.09)	0.92 (0.82-1.03)	0.82 (0.71-0.95)	0.83 (0.70-0.98)	.002	
CMS_{G4}[f]								
0 to 2 (n = 46 732)								
Deaths, No.	313	101	236	317	145	64		
HR (95% CI)[d]	1 [Reference]	1.00 (0.79-1.25)	0.87 (0.73-1.03)	0.82 (0.70-0.97)	0.83 (0.67-1.02)	0.70 (0.53-0.94)	.007	
>2 to 3 (n = 100 609)								
Deaths, No.	692	205	581	756	361	189		
HR (95% CI)[d]	1 [Reference]	0.93 (0.79-1.08)	0.98 (0.87-1.10)	0.86 (0.77-0.96)	0.94 (0.82-1.08)	0.92 (0.78-1.10)	.15	.17
>3 to 4 (n = 121 719)								
Deaths, No.	809	224	639	989	469	273		
HR (95% CI)[d]	1 [Reference]	0.90 (0.78-1.05)	0.90 (0.81-1.00)	0.84 (0.76-0.93)	0.84 (0.74-0.95)	0.86 (0.74-1.00)	.006	
>4 (n = 134 756)								
Deaths, No.	840	256	685	1194	571	341		
HR (95% CI)[d]	1 [Reference]	0.97 (0.85-1.12)	0.89 (0.81-0.99)	0.92 (0.83-1.00)	0.83 (0.74-0.93)	0.78 (0.68-0.90)	<.001	

Abbreviations: CMS_G; Genetic Caffeine Metabolism Score; GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; HR, hazard ratio; NVQ, National Vocational Qualification; SNP, single-nucleotide polymorphism.

[a] Genetic caffeine metabolism scores were weighted by summing the number of alleles multiplied by their β-coefficients (see Methods section). 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. Weighted scores were then calibrated such that $wCMS_{G2}$ and $wCMS_{G4}$ scores ranged from 0 to 4 and from 0 to 8, respectively, with higher scores predicting faster caffeine metabolism.

[b] *P* value for trend corresponds to the χ^2 test statistic for coffee intake as a continuous variable, using the midpoint of each category and a value of 6 for ≥6 cups/d.

[c] *P* value for heterogeneity corresponds to the χ^2 test statistic for the likelihood ratio test comparing the models with and without the interaction term between the coffee (cups/d) and the CMS_G variable of interest (continuous score).

[d] Multivariable model is adjusted for age, sex, detailed smoking history (25-level variable incorporating current smoking status, smoking intensity [current and former smokers]; time since quitting [former smokers], and cigar and pipe use [current and former smokers]); race/ethnicity (white, black, Asian, mixed, or other race); alcohol drinking (never drinker, former drinker, infrequent drinker [<1 drink/wk], occasional drinker [>1 drink/wk but <1 drink/d], moderate daily drinker [1-3 drinks/d], or heavy daily drinker [>3 drinks/d]); general health status (excellent, good, fair, or poor); education level (college or university degree, A levels/AS levels or equivalent, O levels/GCSE or equivalent, CSE or equivalent, NVQ or HND or HNC equivalent, or other professional qualifications); and body mass index (calculated as weight in kilograms divided by height in meters squared) (<18.5, 18.5 to <25.0, 25.0 to <30.0, 30.0 to <35.0, or ≥35.0); physical activity (0, 1-2, 3-4, or ≥5 d of >10 min of moderate- or vigorous-intensity activity); tea intake (0, <1, 1, 2 or 3, 4 or 5, or ≥6 cups/d).

[e] $wCMS_{G2}$ defined using 2 SNPs, *AHR*, *CYP1A2*.

[f] $wCMS_{G4}$ defined using 4 SNPs, *AHR*, *CYP1A2*, *POR*, *CYP2A6*.

Table 5. Association Between Coffee Intake and All-Cause Mortality in the UK Biobank Stratified by Potential Risk Factors

Baseline Characteristic Subgroup	Coffee Consumption, Cups/d						*P* Value	
	0	<1	1	2-3	4-5	≥6	Trend[a]	Heterogeneity[b]
Men (n = 227 115)								
Deaths, No.	2001	611	1579	2486	1239	711		.45
HR (95% CI)[c]	1 [Reference]	0.97 (0.88-1.06)	0.93 (0.87-0.99)	0.88 (0.83-0.94)	0.88 (0.81-0.95)	0.84 (0.77-0.92)	<.001	
Women (n = 27 1019)								
Deaths, No.	1394	383	1115	1612	718	376		
HR (95% CI)[c]	1 [Reference]	0.91 (0.81-1.02)	0.91 (0.84-0.98)	0.89 (0.83-0.96)	0.88 (0.80-0.97)	0.86 (0.76-0.97)	.005	
<55 Years of Age (n = 209 103)								
Deaths, No.	735	168	407	666	386	258		.89
HR (95% CI)[d]	1 [Reference]	0.84 (0.71-1.00)	0.87 (0.77-0.98)	0.86 (0.77-0.96)	0.88 (0.77-1.00)	0.85 (0.72-0.99)	.05	
≥55 Years of Age (n = 289 031)								
Deaths, No.	2660	826	2287	3432	1571	829		
HR (95% CI)[d]	1 [Reference]	0.97 (0.90-1.05)	0.93 (0.88-0.99)	0.89 (0.84-0.94)	0.88 (0.82-0.94)	0.85 (0.78-0.92)	<.001	
Never-Smoker (n = 272 715)								
Deaths, No.	1271	392	1144	1628	634	240		.29
HR (95% CI)[c]	1 [Reference]	0.95 (0.85-1.06)	0.96 (0.88-1.04)	0.94 (0.87-1.01)	0.93 (0.84-1.03)	0.93 (0.80-1.07)	.14	
Former Smoker (n = 172 716)								
Deaths, No.	1392	436	1168	1805	824	395		
HR (95% CI)[d]	1 [Reference]	0.97 (0.87-1.08)	0.92 (0.85-0.99)	0.89 (0.83-0.96)	0.86 (0.79-0.95)	0.83 (0.73-0.93)	<.001	
Current Smoker (n = 52 703)								
Deaths, No.	732	166	382	665	499	452		
HR (95% CI)[d]	1 [Reference]	0.91 (0.77-1.08)	0.88 (0.77-0.99)	0.78 (0.70-0.87)	0.80 (0.71-0.91)	0.76 (0.67-0.87)	<.001	
Excellent/Good Health (n = 368 941)								
Deaths, No.	1561	527	1459	2361	1086	528		.01
HR (95% CI)[c]	1 [Reference]	0.95 (0.86-1.05)	0.89 (0.83-0.96)	0.89 (0.83-0.95)	0.89 (0.82-0.97)	0.89 (0.80-0.99)	.01	
Fair/Poor Health (n = 126 888)								
Deaths, No.	1789	453	1211	1697	862	546		
HR (95% CI)[c]	1 [Reference]	0.94 (0.85-1.04)	0.94 (0.87-1.01)	0.86 (0.80-0.93)	0.83 (0.76-0.91)	0.78 (0.70-0.86)	<.001	
BMI 18.5 to <25.0 (n = 156 785)								
Deaths, No.	886	282	749	1050	457	281		.19
HR (95% CI)[c]	1 [Reference]	0.99 (0.86-1.13)	0.93 (0.84-1.03)	0.88 (0.80-0.97)	0.88 (0.78-0.99)	0.88 (0.76-1.02)	.01	
BMI 25.0 to <30.0 (n = 209 107)								
Deaths, No.	1281	366	1046	1673	777	404		
HR (95% CI)[c]	1 [Reference]	0.88 (0.78-0.99)	0.88 (0.81-0.96)	0.86 (0.80-0.93)	0.85 (0.77-0.93)	0.82 (0.73-0.93)	<.001	
BMI ≥30.0 (n = 120 665)								
Deaths, No.	968	8104	775	1162	611	330		
HR (95% CI)[c]	1 [Reference]	1.00 (0.88-1.14)	1.03 (0.94-1.13)	0.93 (0.85-1.02)	0.91 (0.81-1.01)	0.83 (0.73-0.95)	.001	
No History of Diabetes (n = 470 575)[e]								
Deaths, No.	2867	867	2348	3575	1695	922		.18
HR (95% CI)[c]	1 [Reference]	0.95 (0.88-1.03)	0.92 (0.87-0.97)	0.88 (0.84-0.93)	0.88 (0.82-0.94)	0.83 (0.77-0.90)	<.001	

(continued)

used in Mendelian randomization studies of coffee and health.[26,27] In the present study, we observed a weak positive association between $wCMS_{G4}$ and all-cause mortality, which may indicate that slower caffeine metabolism is beneficial. However, results of these Mendelian randomization studies warrant careful interpretation because CMS_G explains only a very small proportion of the variance in coffee intake[25] and, importantly, also reflects biological exposure to caffeine,[24,28] which is how we have applied it in the present study.

The UK Biobank presented a unique opportunity to assess potential differences between drinking instant vs ground coffee because 55% of coffee drinkers reported usually drinking instant coffee. Associations for ground coffee and all-cause mortality were generally stronger than those for instant coffee. This observation may be explained by residual confounding owing to unmeasured or poorly measured confounders. For example, instant coffee was more common among participants without a college degree than among college graduates. Alternatively, instant coffees have been shown to have lower amounts of bioactive compounds, including polyphenols, than ground coffees,[29] which may have an effect on observed associations. Mechanisms hypothesized to explain the potential protective effect of coffee drinking on mortality risk include reduced inflammation,[30] improved insulin sensitivity,[31] and effects on liver enzyme levels[31] and endothelial function.[32] Further studies with more detailed information on coffee type and preparation may provide insight into the mechanisms underlying coffee-chronic disease associa-

Table 5. Association Between Coffee Intake and All-Cause Mortality in the UK Biobank Stratified by Potential Risk Factors (continued)

Baseline Characteristic Subgroup	Coffee Consumption, Cups/d						*P* Value	
	0	<1	1	2-3	4-5	≥6	Trend[a]	Heterogeneity[b]
History of Diabetes (n = 26 063)[c]								
Deaths, No.	505	124	336	503	253	159		
HR (95% CI)[c]	1 [Reference]	0.89 (0.73-1.09)	0.91 (0.79-1.05)	0.86 (0.75-0.98)	0.82 (0.69-0.96)	0.88 (0.72-1.06)	.06	
No History of Cancer, Heart Attack, or Stroke (n = 447 064)[f]								
Deaths, No.	2325	684	1831	2841	1413	781		.19
HR (95% CI)[c]	1 [Reference]	0.94 (0.86-1.02)	0.88 (0.83-0.94)	0.85 (0.80-0.90)	0.87 (0.81-0.93)	0.84 (0.77-0.92)	<.001	
History of Cancer, Heart Attack, or Stroke (n = 51 070)[f]								
Deaths, No.	1070	310	863	1257	544	306		
HR (95% CI)[c]	1 [Reference]	0.96 (0.84-1.09)	1.00 (0.92-1.10)	1.00 (0.92-1.09)	0.91 (0.82-1.02)	0.87 (0.75-0.99)	.03	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; HR, hazard ratio; NVQ, National Vocational Qualification.

[a] *P* value for trend corresponds to the χ^2 test statistic for coffee intake as a continuous variable, using the midpoint of each category and a value of 6 for ≥6 cups/d.

[b] *P* value for heterogeneity corresponds to the χ^2 test statistic for the likelihood ratio test comparing the models with and without the interaction term between coffee (continuous) and the stratifying variable of interest (categorical).

[c] Multivariable model is adjusted for age, sex, detailed smoking history (25-level variable incorporating current smoking status, smoking intensity [current and former smokers]; time since quitting [former smokers], and cigar and pipe use [current and former smokers]); race/ethnicity (white, black, Asian, mixed, or other race); alcohol drinking (never drinker, former drinker, infrequent drinker [<1 drink/wk], occasional drinker [>1 drink/wk but <1 drink/d], moderate daily drinker [1-3 drinks/d], or heavy daily drinker [>3 drinks/d]); general health status (excellent, good, fair, or poor); education level (college or university degree, A levels/AS levels or equivalent, O levels/GCSE or equivalent, CSE, NVQ or HND or HNC equivalent, or other professional qualifications); and body mass index (calculated as weight in kilograms divided by height in meters squared) (<18.5, 18.5 to <25.0, 25.0 to <30.0, 30.0 to <35.0, or ≥35.0); physical activity (0, 1-2, 3-4, or ≥5 d of >10 min of moderate- or vigorous-intensity activity); tea intake (0, <1, 1, 2 or 3, 4 or 5, or ≥6 cups/d) less the stratifying variable.

[d] Age and smoking subgroups (ie, former and current smokers) are adjusted for all variables including age and detailed former or current smoking.

[e] Self-reported diagnosis of diabetes by a physician.

[f] Self-reported diagnosis of cancer, other than nonmelanoma skin cancer, or heart attack, or stroke by a physician.

tions. For example, information on coffee preparation (ie, filtered, cappuccino, espresso, and latte) is available on a subset of approximately 70 000 UK Biobank participants who completed 24-hour dietary recalls at baseline and will be useful as the cohort matures.

Strengths and Limitations

Strengths of this study include its prospective design, large sample size, wide range of coffee intake, and availability of genotype and coffee type data. Limitations include the study's low participation rate, approximately 5.5%; consequently, the cohort is not demographically representative of the general UK population, with evidence of a "healthy volunteer" selection bias.[22] Nevertheless, valid estimation of exposure-disease relationships does not require a representative population,[22] and our results reflect those from prior studies in different populations worldwide. Despite the large size of the cohort, there were relatively few deaths from specific types of cancer and cardiovascular disease. However, future analyses of these end points will be possible as the UK Biobank cohort matures.

Conclusions

In the very large UK Biobank cohort, coffee drinking was associated inversely with all-cause mortality, including in those drinking at least 8 cups per day, in both slow and fast metabolizers of caffeine, and in consumers of ground, instant, and decaffeinated coffee. Our results are based on observational data and should be interpreted with caution. Nevertheless, these results provide further evidence that coffee drinking can be part of a healthy diet and may provide reassurance to those who drink coffee and enjoy it.

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Study concept and design: Loftfield, Yu, Sinha, Freedman.
Acquisition, analysis, or interpretation of data: Loftfield, Cornelis, Caporaso, Yu, Freedman.
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REFERENCES

1. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. *Circulation*. 2014;129(6):643-659.

2. Larsson SC, Orsini N. Coffee consumption and risk of stroke: a dose-response meta-analysis of prospective studies. *Am J Epidemiol*. 2011;174(9):993-1001.

3. Ding M, Bhupathiraju SN, Chen M, van Dam RM, Hu FB. Caffeinated and decaffeinated coffee consumption and risk of type 2 diabetes: a systematic review and a dose-response meta-analysis. *Diabetes Care*. 2014;37(2):569-586.

4. Liu R, Guo X, Park Y, et al. Caffeine intake, smoking, and risk of Parkinson disease in men and women. *Am J Epidemiol*. 2012;175(11):1200-1207.

5. Bravi F, Bosetti C, Tavani A, Gallus S, La Vecchia C. Coffee reduces risk for hepatocellular carcinoma: an updated meta-analysis. *Clin Gastroenterol Hepatol*. 2013;11(11):1413-1421.e1.

6. Gan Y, Wu J, Zhang S, et al. Association of coffee consumption with risk of colorectal cancer: a meta-analysis of prospective cohort studies. *Oncotarget*. 2017;8(12):18699-18711.

7. Zhou Q, Luo ML, Li H, Li M, Zhou JG. Coffee consumption and risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. *Sci Rep*. 2015;5:13410.

8. Gapstur SM, Anderson RL, Campbell PT, et al. Associations of coffee drinking and cancer mortality in the Cancer Prevention Study-II. *Cancer Epidemiol Biomarkers Prev*. 2017;26(10):1477-1486.

9. Park SY, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW. Association of coffee consumption with total and cause-specific mortality among nonwhite populations. *Ann Intern Med*. 2017;167(4):228-235.

10. Gunter MJ, Murphy N, Cross AJ, et al. Coffee drinking and mortality in 10 European countries: a multinational cohort study. *Ann Intern Med*. 2017;167(4):236-247.

11. Freedman ND, Park Y, Abnet CC, Hollenbeck AR, Sinha R. Association of coffee drinking with total and cause-specific mortality. *N Engl J Med*. 2012;366(20):1891-1904.

12. Loftfield E, Freedman ND, Graubard BI, et al. Association of coffee consumption with overall and cause-specific mortality in a large US prospective cohort study. *Am J Epidemiol*. 2015;182(12):1010-1022.

13. Ding M, Satija A, Bhupathiraju SN, et al. Association of coffee consumption with total and cause-specific mortality in 3 large prospective cohorts. *Circulation*. 2015;132(24):2305-2315.

14. Crippa A, Discacciati A, Larsson SC, Wolk A, Orsini N. Coffee consumption and mortality from all causes, cardiovascular disease, and cancer: a dose-response meta-analysis. *Am J Epidemiol*. 2014;180(8):763-775.

15. Tamakoshi A, Lin Y, Kawado M, Yagyu K, Kikuchi S, Iso H; JACC Study Group. Effect of coffee consumption on all-cause and total cancer mortality: findings from the JACC study. *Eur J Epidemiol*. 2011;26(4):285-293.

16. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ*. 2017;359:j5024.

17. Dietary Guidelines for Americans Advisory Committee. *Scientific Report of the 2015 Dietary Guidelines Advisory Committee*. Washington, DC: USDA and US Department of Health and Human Services; 2015.

18. Cornelis MC, Byrne EM, Esko T, et al; Coffee and Caffeine Genetics Consortium; International Parkinson's Disease Genomics Consortium (IPDGC); North American Brain Expression Consortium (NABEC); UK Brain Expression Consortium (UKBEC). Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption. *Mol Psychiatry*. 2015;20(5):647-656.

19. Cornelis MC, El-Sohemy A, Kabagambe EK, Campos H. Coffee, CYP1A2 genotype, and risk of myocardial infarction. *JAMA*. 2006;295(10):1135-1141.

20. Palatini P, Ceolotto G, Ragazzo F, et al. CYP1A2 genotype modifies the association between coffee intake and the risk of hypertension. *J Hypertens*. 2009;27(8):1594-1601.

21. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779.

22. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol*. 2017;186(9):1026-1034.

23. Bycroft C, Freeman C, Petkova D, et al. Genome-wide genetic data on ~500,000 UK Biobank participants [preprint]. bioRxiv. 2017. https://www.biorxiv.org/content/early/2017/07/20/166298. Accessed April 26, 2018.

24. Cornelis MC, Kacprowski T, Menni C, et al; Swiss Kidney Project on Genes in Hypertension (SKIPOGH) team. Genome-wide association study of caffeine metabolites provides new insights to caffeine metabolism and dietary caffeine-consumption behavior. *Hum Mol Genet*. 2016;25(24):5472-5482.

25. Taylor AE, Davey Smith G, Munafò MR. Associations of coffee genetic risk scores with consumption of coffee, tea, and other beverages in the UK Biobank. *Addiction*. 2018;113(1):148-157.

26. Nordestgaard AT, Thomsen M, Nordestgaard BG. Coffee intake and risk of obesity, metabolic syndrome and type 2 diabetes: a Mendelian randomization study. *Int J Epidemiol*. 2015;44(2):551-565.

27. Nordestgaard AT, Nordestgaard BG. Coffee intake, cardiovascular disease and all-cause mortality: observational and Mendelian randomization analyses in 95 000-223 000 individuals. *Int J Epidemiol*. 2016;45(6):1938-1952.

28. van Dam RM. Can "omics" studies provide evidence for causal effects of coffee consumption on risk of type 2 diabetes? *J Intern Med*. 2018.

29. Rodrigues NP, Bragagnolo N. Identification and quantification of bioactive compounds in coffee brews by HPLC-DAD-MSn. *J Food Compos Anal*. 2013;32(2):105-115.

30. Loftfield E, Shiels MS, Graubard BI, et al. Associations of coffee drinking with systemic immune and inflammatory markers. *Cancer Epidemiol Biomarkers Prev*. 2015;24(7):1052-1060.

31. Jacobs S, Kröger J, Floegel A, et al. Evaluation of various biomarkers as potential mediators of the association between coffee consumption and incident type 2 diabetes in the EPIC-Potsdam Study. *Am J Clin Nutr*. 2014;100(3):891-900.

32. Lopez-Garcia E, van Dam RM, Qi L, Hu FB. Coffee consumption and markers of inflammation and endothelial dysfunction in healthy and diabetic women. *Am J Clin Nutr*. 2006;84(4):888-893.