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Association of Sugar-Sweetened, Artificially Sweetened, and Unsweetened Coffee Consumption With All-Cause and Cause-Specific Mortality

A Large Prospective Cohort Study

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Background: Previous observational studies have suggested an association between coffee intake and reduced risk for death, but these studies did not distinguish between coffee consumed with sugar or artificial sweeteners and coffee consumed without.

Objective: To evaluate the associations of consumption of sugar-sweetened, artificially sweetened, and unsweetened coffee with all-cause and cause-specific mortality.

Design: Prospective cohort study.

Setting: Data were extracted from the UK Biobank.

Participants: A total of 171 616 participants (mean age, 55.6 years [SD, 7.9]) without cardiovascular disease (CVD) or cancer at baseline were eligible. Baseline demographic, lifestyle, and dietary data from the UK Biobank were used, with follow-up beginning in 2009 and ending in 2018.

Measurements: Dietary consumption of sugar-sweetened, artificially sweetened, and unsweetened coffee was self-reported. All-cause, cancer-related, and CVD-related mortality were estimated.

Results: During a median follow-up of 7.0 years, 3177 deaths were recorded (including 1725 cancer deaths and 628 CVD deaths). Cox models with penalized splines showed U-shaped associations of unsweetened coffee, sugar-sweetened coffee, and artificially sweetened coffee with mortality. Compared with nonconsumers, consumers of various amounts of unsweetened coffee (>0 to 1.5, >1.5 to 2.5, >2.5 to 3.5, >3.5 to 4.5, and >4.5 drinks/d) had lower risks for all-cause mortality after adjustment for lifestyle, sociodemographic, and clinical factors, with respective hazard ratios of 0.79 (95% CI, 0.70 to 0.90), 0.84 (CI, 0.74 to 0.95), 0.71 (CI, 0.62 to 0.82), 0.71 (CI, 0.60 to 0.84), and 0.77 (CI, 0.65 to 0.91); the respective estimates for consumption of sugar-sweetened coffee were 0.91 (CI, 0.78 to 1.07), 0.69 (CI, 0.57 to 0.84), 0.72 (CI, 0.57 to 0.91), 0.79 (CI, 0.60 to 1.06), and 1.05 (CI, 0.82 to 1.36). The association between artificially sweetened coffee and mortality was less consistent. The association of coffee drinking with mortality from cancer and CVD was largely consistent with that with all-cause mortality. U-shaped associations were also observed for instant, ground, and decaffeinated coffee.

Limitation: Exposure assessed at baseline might not capture changes in intake over time.

Conclusion: Moderate consumption of unsweetened and sugar-sweetened coffee was associated with lower risk for death.

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Coffee is among the most widely consumed beverages worldwide, and interest in its health effects has been long-standing. Previous observational studies have suggested an association between coffee intake and reduced risk for death (1–5), but they did not distinguish between coffee consumed with sugar or artificial sweeteners and coffee consumed without. Despite health warnings, the consumption of sugar remains high in many regions, and the growing consumption of sugar or sweetener in coffee has raised concerns. Previous observational evidence supports a link between the consumption of sugar-sweetened beverages (SSBs) and chronic diseases (6–14). Some research has also suggested the need to discourage the consumption of artificially sweetened beverages (ASBs) despite their containing few or no calories (6–8, 10, 12, 13, 15). In addition to these uncertainties, previous studies are limited in their ability to examine individual coffee types (including instant, ground, and decaffeinated coffee), and the effects of sugar or sweetener added to different coffee types are unknown.

Because of limited evidence of the effect of sugar-sweetened and artificially sweetened coffee intake on health outcomes, more studies investigating the long-term effects of such intake are needed. Therefore, the objectives of this study were to evaluate the associations of sugar-sweetened, artificially sweetened, and unsweetened coffee with all-cause and cause-specific mortality and to further

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evaluate the associations between coffee types (including instant, ground, and decaffeinated coffee) and mortality.

METHODS

Study Design

We used data from the UK Biobank (application 43795), a large prospective cohort study of 502 524 participants aged 37 to 73 years recruited from 22 study centers across the United Kingdom (England, Wales, and Scotland) between 2006 and 2010. Participants completed a touchscreen questionnaire, face-to-face interviews, and physical measurements and provided biological samples, as described in detail elsewhere (16, 17). They provided informed consent to have their records linked to hospital admissions, cancer registries, and death registries.

For this analysis, participants who had completed the online 24-hour dietary recall questionnaire on at least 1 occasion were eligible for inclusion. In total, 211 020 persons completed at least 1 dietary questionnaire. We excluded participants with an implausible energy intake (defined as those in the highest or lowest 1% of the distribution of the ratio of energy intake to estimated energy requirement; *n* = 4236 [2.0%]), those with cancer (*n* = 21 649 [10.3%]) at baseline, those with cardiovascular disease (CVD) (including stroke and myocardial infarction; *n* = 6395 [3.0%]) at baseline, those who subsequently withdrew from the study (*n* = 504 [0.2%]), and those who had overlap across unsweetened, sugar-sweetened, and artificially sweetened coffee (*n* = 6620 [3.1%]), leaving 171 616 participants (81.3%) eligible for inclusion in the study (Appendix Figure, available at Annals.org).

Assessment of Coffee Consumption

Dietary information was collected using a web-based 24-hour dietary recall questionnaire called the Oxford WebQ, which is similar to a 24-hour dietary recall assessing the types and quantities of foods consumed, including beverages and daily nutrient intake, and has been validated in detail elsewhere (18). Participants were invited to complete the questionnaire on 5 occasions over 1 year to account for seasonal variations in dietary intake between April 2009 and June 2012.

In each 24-hour dietary recall, participants indicated how many drinks of coffee they had had in the previous 24 hours. If participants drank coffee, they could report whether they added sugar or artificial sweeteners (any brand) and how many teaspoons were added. Each dietary recall had 4 groups of coffee consumers: nonconsumers, unsweetened coffee consumers, sugar-sweetened coffee consumers, and artificially sweetened coffee consumers. Because participants could complete the 24-hour dietary recall up to 5 times, we classified a participant drinking coffee at any 1 dietary recall as a coffee consumer; all others were classified as nonconsumers. We classified a participant drinking the same kind of coffee (unsweetened, sugar-sweetened, or artificially sweetened) in different dietary recalls as a sole consumer; others were classified as overlapped consumers. Coffee consumer categories are shown in Supplement Table 1 (available at Annals.org). We excluded 6620 overlapped consumers. For sole consumers, we calculated an average number of drinks across multiple dietary recalls as a marker of habitual intake. For example, if a participant completed 3 dietary recalls in total and drank 1, 2, and 1 drinks of unsweetened coffee in the 3 recalls, then an average number of drinks of unsweetened coffee per day was 1.33.

Coffee consumers were asked about the types of coffee they usually drank and could select 1 of 7 mutually exclusive responses (0.5, 1, 2, 3, 4, 5, or 6 or more drinks) for each type, including instant coffee, ground coffee (such as filter or cappuccino), and decaffeinated coffee (any type). One drink was equal to approximately 250 mL. The online diet questionnaire provided some specifications for regular drinks (for example, mug or cup) to reduce confusion about size. If participants reported drinking more than 10 drinks from all types of coffee in total, they were asked to confirm the response.

Assessment of Outcomes

Mortality data (19) were obtained from death certificates according to the National Health Service Information Centre (England and Wales) and the National Health Service Central Register Scotland (Scotland). Mortality data were available through 25 February 2018 for England and Wales and through 28 February 2017 for Scotland. We censored participants in the mortality analysis at this date or the date of death, whichever occurred first. Outcomes were classified using the International Classification of Diseases, 10th Revision. For this analysis, we measured all-cause mortality and mortality due to CVD (codes I00 to I99) and cancer (codes C00 to D48).

Assessment of Covariates

We used the baseline questionnaire to assess the following potential confounders: age, sex, ethnicity, Townsend deprivation index (TDI), education level, smoking status, pack-years of smoking, physical activity over the past week, body mass index, waist circumference, hypertension, diabetes, depression, family history of CVD, family history of cancer, long-standing illness, cholesterol-lowering drug use, blood pressure drug use, vitamin and mineral supplement use, and dietary intake of total energy, total sugar, fresh fruit, vegetables, red meat, processed meat, alcohol, milk, tea, SSBs, and ASBs. The TDI was used as an indicator of socioeconomic status, and negative TDI values indicated relative affluence. The general definition of a pack-year of smoking was the number of cigarettes smoked per day divided by 20 and multiplied by the number of years of smoking. Hypertension was defined as a self-reported history of hypertension, systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or use of antihypertensive drugs. Long-standing illness was self-reported using the question "Do you have any long-standing illness, disability, or infirmity?" (yes or no) to assess overall health. According to the guidelines of the International Physical Activity Questionnaire (20), we categorized participants into low, moderate, and high activity level groups based on categorical criteria, which are shown in the footnotes of Supplement Table 2 (available at Annals.org). The details of these assessments can be found on the UK Biobank website (www.ukbiobank.ac.uk).

Statistical Analysis

Detailed information on the missing covariates is presented in Supplement Table 2, and we used multiple imputation by chained equations to impute any missing covariate values with 10 data sets. All variables, including outcomes, were included in the multiple imputation model. Baseline characteristics are presented as mean (SD) for continuous variables and number (percentage) for categorical variables. Pearson correlations were used to demonstrate consistency across multiple assessments of coffee consumption, and SDs were used to describe variation (Supplement Table 3, available at Annals.org). Consumption of sugar added to coffee, that of sweeteners added to coffee, and that of total sugar across multiple 24-hour dietary recalls are presented as mean (SD) (Supplement Table 4, available at Annals.org).

Dose–response relationships were examined using nonparametrically restricted cubic spline regression with knots at the 25th, 50th, and 75th percentiles between coffee consumption and mortality. The consumption was then categorized into the following 5 groups: greater than 0 to 1.5 drinks/d, greater than 1.5 to 2.5 drinks/d, greater than 2.5 to 3.5 drinks/d, greater than 3.5 to 4.5 drinks/d, and greater than 4.5 drinks/day—equivalent to averages of 1, 2, 3, 4, and 5 or more drinks/d, respectively. Cox proportional hazards regression was used to estimate hazard ratios and 95% CIs for the prospective association of coffee consumption with mortality. The proportional hazards assumption was tested using Schoenfeld residuals. We adjusted for baseline age (continuous), sex (male or female), TDI (continuous), education level (degree or no degree), ethnicity (White or other), smoking status (current, former, or never), pack-years of smoking (continuous), physical activity level (low, moderate, or high), body mass index (continuous), waist circumference (continuous), hypertension (yes or no), diabetes (yes or no), depression (yes or no), family history of CVD (yes or no), family history of cancer (yes or no), long-standing illness (yes or no), cholesterol-lowering drug use (yes or no), blood pressure drug use (yes or no), vitamin and mineral supplement use (yes or no [vitamin A, B, C, D, or E; folic acid; or multivitamins or minerals]), and intake of total energy (including sugar added to coffee), total sugar (including sugar added to coffee), fresh fruit, vegetables, red meat, processed meat, alcohol, tea, milk, SSBs, and ASBs.

We did the following sensitivity analyses to assess the robustness of the results. We excluded participants who had an outcome event during the first 2 years of follow-up. We excluded a coffee measurement if a participant reported having an unusual coffee consumption day on any of 5 occasions to maximize the representation of participants' typical dietary habits. We excluded participants with missing covariates. We removed the sugar added to coffee from total sugar and the energy it produced from total energy. We excluded participants who were drinking coffee the year prior but not drinking coffee the day before. We additionally adjusted for environmental factors, including particulate matter less than 2.5 μm in diameter, between 2.5 and 10 μm in diameter, and greater than 10 μm in diameter; nitrogen dioxide; average 24-hour sound level of noise pollution; proximity to a major road; green space percentage; and distance to coast. Last, the E-value (21) was estimated to examine the magnitude of an unmeasured confounding factor that could affect the association between coffee consumption and mortality by random chance.

Analyses were done using SAS software, version 9.4 for Windows (SAS Institute). Statistical tests were 2-sided, and *P* values less than 0.05 were considered statistically significant.

Role of the Funding Source

The funders had no influence on the study design, conduct, or reporting.

RESULTS

Baseline Characteristics

Among 171 616 participants, 130 132 (75.8%) were coffee consumers. Unsweetened coffee (55.4%) was the most commonly consumed, followed by sugar-sweetened coffee (14.3%) and artificially sweetened coffee (6.1%). Consumers of sugar-sweetened and artificially sweetened coffee added an average of 1.1 teaspoons (SD, 0.6) and 1.4 teaspoons (SD, 0.6) of sugar and sweetener, respectively. Nonconsumers of coffee were more likely to be drinking tea. Sugar-sweetened coffee consumers were more likely to be male, from a lower social class, and current smokers and generally had less healthy diets. Artificially sweetened coffee consumers were more likely to be older, former heavy smokers, and obese and to report hypertension, diabetes, depression, and a family history of CVD. Unsweetened coffee consumers were of a higher social class and generally had healthier diets (Table 1).

Coffee Consumption and All-Cause Mortality

During a median follow-up of 7.0 years (IQR, 6.6 to 7.8 years; total person-years, 1 212 322), we recorded 3177 deaths (including 1725 cancer deaths and 628 CVD deaths). Cox models with penalized splines showed statistically significant U-shaped associations for unsweetened coffee and sugar-sweetened coffee with all-cause mortality ($P < 0.001$), and the U-shaped association was not statistically significant for artificially sweetened coffee (Figure). When we categorized coffee consumption into 5 groups, compared with nonconsumers, consumers of different amounts of unsweetened coffee (>0 to 1.5, >1.5 to 2.5, >2.5 to 3.5, >3.5 to 4.5, and >4.5 drinks/d) had lower risks for all-cause mortality after adjustment for lifestyle, sociodemographic, and clinical factors, with respective hazard ratios of 0.79 (95% CI, 0.70 to 0.90), 0.84 (CI, 0.74 to 0.95), 0.71 (CI, 0.62 to 0.82), 0.71 (CI, 0.60 to 0.84), and 0.77 (CI, 0.65 to 0.91); the respective estimates for consumption of sugar-sweetened coffee were 0.91 (CI, 0.78 to 1.07), 0.69 (CI, 0.57 to 0.84), 0.72 (CI, 0.57 to 0.91), 0.79 (CI, 0.60 to 1.06), and 1.05 (CI, 0.82 to 1.36) (Table 2). Findings for instant, ground, and decaffeinated coffee were consistent with our primary results (Table 3). The association between artificially sweetened coffee and mortality was less consistent and conclusive, with wide 95% CIs that included 1.0 in some cases (Figure and Tables 2 and 3).

Table 1. Baseline Characteristics of Participants

Characteristic	Total	Nonconsumers	Coffee Consumers		
			Unsweetened	Sugar-Sweetened	Artificially Sweetened
Participants, *n (%)*	171 616 (100.0)	41 484 (24.2)	95 135 (55.4)	24 607 (14.3)	10 390 (6.1)
Mean age (SD), *y*	55.6 (7.9)	54.2 (8.0)	56.0 (7.7)	55.7 (8.3)	57.1 (7.8)
Male sex, *n (%)*	76 527 (44.6)	17 343 (41.8)	39 803 (41.8)	14 795 (60.1)	4586 (44.1)
Mean Townsend deprivation index (SD)	−1.6 (2.9)	−1.3 (3.0)	−1.8 (2.8)	−1.4 (3.0)	−1.5 (2.9)
Ethnicity, *n (%)*					
White	163 674 (95.7)	37 918 (91.8)	92 714 (97.8)	23 038 (94.0)	10 004 (96.6)
Other	7322 (4.3)	3388 (8.2)	2114 (2.2)	1463 (6.0)	357 (3.4)
Education, *n (%)*					
Degree	74 633 (43.7)	15 686 (38.0)	47 054 (49.6)	8700 (35.6)	3193 (30.9)
No degree	96 179 (56.3)	25 535 (62.0)	47 761 (50.4)	15 743 (64.4)	7140 (69.1)
Smoking status, *n (%)*					
Never	99 047 (57.9)	25 667 (62.1)	56 206 (59.2)	12577 (51.3)	4597 (44.3)
Former	58 920 (34.4)	12 881 (31.1)	32 932 (34.7)	8467 (34.5)	4640 (44.8)
Current	13 222 (7.7)	2815 (6.8)	5794 (6.1)	3486 (14.2)	1127 (10.9)
Mean pack-years of smoking for current or former smokers (SD)	20.0 (16.4)	20.5 (17.0)	18.0 (15.0)	22.8 (17.3)	24.5 (18.7)
Physical activity level, *n (%)*					
Low	31 352 (18.3)	8197 (19.8)	16 404 (17.3)	4632 (18.9)	2119 (20.5)
Moderate	72 209 (42.2)	16 908 (41.0)	41 102 (43.3)	9930 (40.5)	4269 (41.2)
High	67 550 (39.5)	16 182 (39.2)	37 442 (39.4)	9960 (40.6)	3966 (38.3)
Mean BMI (SD), *kg/m²*	26.9 (4.6)	27.0 (4.9)	26.7 (4.5)	26.5 (4.2)	28.8 (5.0)
Mean waist circumference (SD), *cm*	89.1 (13.1)	89.0 (13.3)	88.5 (13.0)	90.1 (12.0)	93.6 (14.0)
Hypertension, *n (%)*	97 312 (56.7)	22 891 (55.2)	53 447 (56.2)	14 355 (58.3)	6619 (63.7)
Diabetes, *n (%)*	7254 (4.2)	1855 (4.5)	3847 (4.0)	414 (1.7)	1138 (11.0)
Depression, *n (%)*	17 747 (10.3)	4743 (11.4)	9317 (9.8)	2489 (10.1)	1198 (11.5)
Family history of CVD, *n (%)*	44 567 (26.0)	10 243 (24.7)	25 270 (26.6)	6252 (25.4)	2802 (27.0)
Family history of cancer, *n (%)*	39 739 (23.2)	9092 (21.9)	22 540 (23.7)	5799 (23.6)	2308 (22.2)
Long-standing illness, *n (%)*	45 958 (27.3)	12 048 (29.7)	23 677 (25.3)	6563 (27.3)	3670 (36.1)
Cholesterol-lowering drug use, *n (%)*	25 429 (14.8)	5618 (13.5)	13 649 (14.4)	3572 (14.5)	2590 (24.9)
Blood pressure drug use, *n (%)*	30 266 (17.6)	7310 (17.6)	16 074 (16.9)	4177 (17.0)	2705 (26.0)
Vitamin and mineral supplement use, *n (%)*	55 500 (32.4)	13 797 (33.3)	30 530 (32.1)	7429 (30.2)	3744 (36.1)
Mean intake (SD)					
Energy, *kcal/d*	2098.8 (565.2)	2054.5 (589.5)	2086.3 (541.2)	2235.6 (589.4)	2066.6 (574.0)
Total sugar, *g/d*	119.5 (47.0)	119.2 (50.1)	115.8 (43.8)	136.4 (49.8)	114.9 (47.3)
Fruit, *servings/d*	2.3 (1.5)	2.2 (1.6)	2.4 (1.5)	1.9 (1.5)	2.2 (1.5)
Vegetables, *servings/d*	4.9 (3.2)	4.9 (3.4)	5.1 (3.2)	4.5 (3.1)	5.0 (3.3)
Red meat, *servings/d*	0.6 (0.7)	0.5 (0.7)	0.6 (0.7)	0.6 (0.7)	0.6 (0.8)
Processed meat, *servings/d*	1.0 (1.4)	0.8 (1.4)	1.0 (1.4)	1.0 (1.5)	1.0 (1.5)
Alcohol, *g/d*	18.6 (21.4)	15.4 (21.7)	20.1 (20.9)	19.0 (22.1)	17.6 (21.7)
Milk, *drinks/d**	0.1 (0.4)	0.1 (0.4)	0.1 (0.3)	0.1 (0.4)	0.1 (0.4)
Tea, *drinks/d**	2.9 (2.1)	3.9 (2.1)	2.7 (2.0)	2.5 (1.9)	2.2 (1.9)
SSBs, *drinks/d**	0.5 (0.9)	0.6 (1.0)	0.5 (0.9)	0.7 (1.0)	0.6 (1.0)
ASBs, *drinks/d**	0.3 (0.7)	0.3 (0.8)	0.3 (0.7)	0.2 (0.6)	0.6 (1.0)
Coffee on average in past year, *(drinks/d)**	2.0 (2.0)	0.4 (0.9)	2.6 (1.9)	2.3 (2.0)	2.8 (2.1)
Coffee, *drinks/d**	1.8 (1.5)	–	2.4 (1.3)	2.2 (1.3)	2.5 (1.4)
Instant	1.1 (1.4)	–	1.5 (1.5)	1.5 (1.4)	2.0 (1.5)
Ground	0.6 (0.9)	–	0.9 (1.0)	0.6 (0.9)	0.5 (0.9)
Decaffeinated	0.3 (0.9)	–	0.4 (1.1)	0.3 (0.8)	0.6 (1.2)
Mean sweetener added to coffee (SD), *teaspoons/d*					
Sugar	0.2 (0.4)	–	–	1.1 (0.6)	–
Artificial sweetener	0.1 (0.4)	–	–	–	1.4 (0.6)
Mean completed 24-h dietary recalls (SD), *n*	2.2 (1.2)	1.9 (1.1)	2.3 (1.2)	2.1 (1.2)	2.1 (1.1)

ASB = artificially sweetened beverage; BMI = body mass index; CVD = cardiovascular disease; SSB = sugar-sweetened beverage.
* 1 drink is equal to approximately 250 mL.

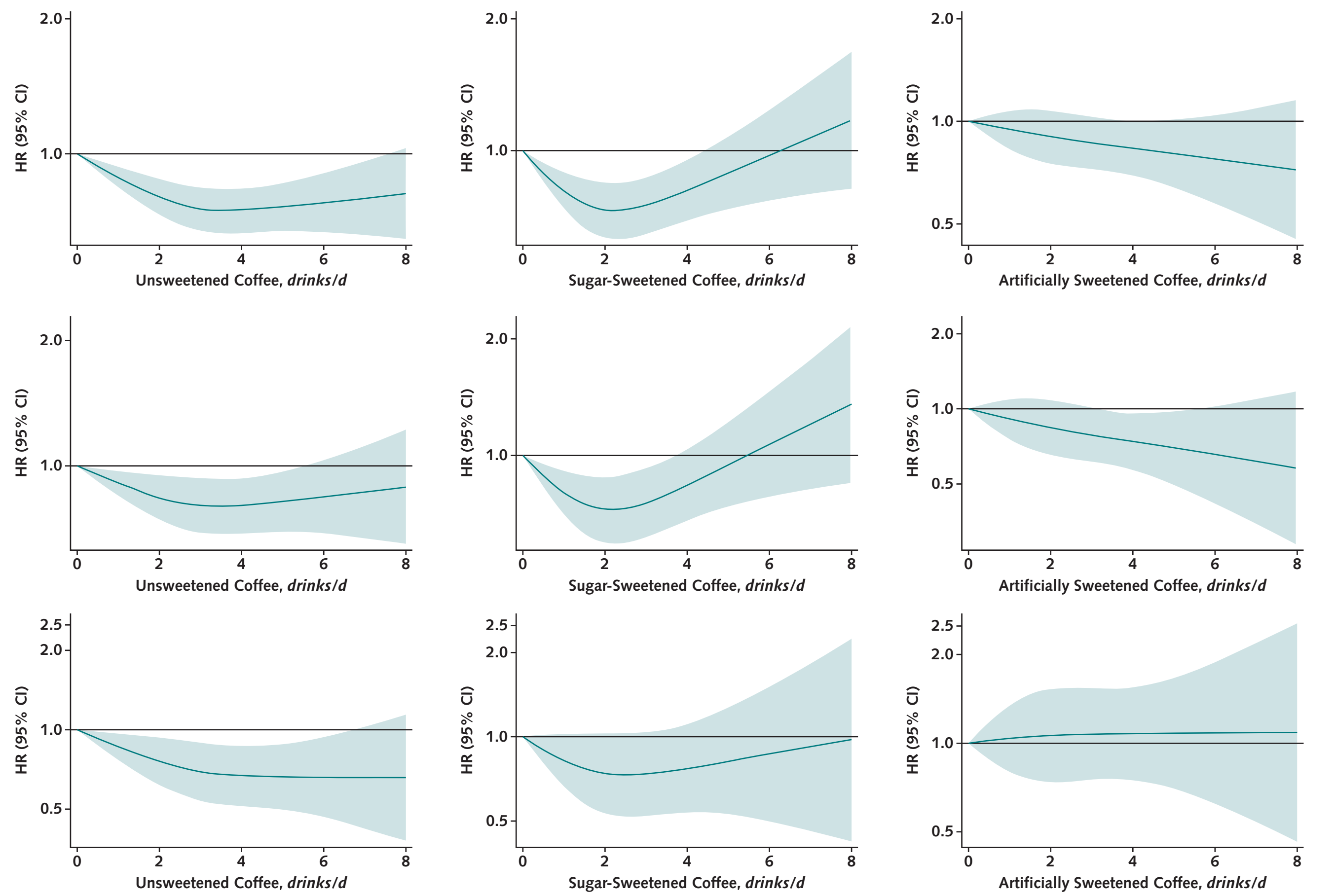
Coffee Consumption and Cause-Specific Mortality

Among 3177 participants with an ascertained cause of death, 1725 died of cancer and 628 of CVD. The association of coffee drinking with cancer and CVD mortality was largely consistent with that with all-cause mortality (**Figure** and **Table 2**). U-shaped associations of unsweetened coffee with cancer and CVD mortality were statistically significant ($P < 0.001$). For sugar-sweetened and artificially sweetened coffee, the inverse associations were observed only for cancer mortality in some cases, but the 95% CIs for artificially sweetened coffee were wider (**Figure** and **Table 2**).

Subgroup and Sensitivity Analyses

The **Supplement Figure** (available at Annals.org) presents results from our subgroup analyses, which did not suggest effect modification, except potentially by alcohol consumption and sex for some outcomes. **Supplement Tables 5** to **10** (available at Annals.org) present results from our sensitivity

Figure. Dose-response associations of coffee consumption with all-cause (*top*), cancer (*middle*), and CVD (*bottom*) mortality.



Multivariable Cox regression model with penalized splines adjusted for age, sex, Townsend deprivation index, education level, ethnicity, smoking status, pack-years of smoking, physical activity level, body mass index, waist circumference, hypertension, diabetes, depression, family history of CVD, family history of cancer, long-standing illness, cholesterol-lowering drug use, blood pressure drug use, vitamin and mineral supplement use, and intake of total energy, total sugar, fresh fruit, vegetables, red meat, processed meat, alcohol, tea, milk, sugar-sweetened beverages, and artificially sweetened beverages. CVD = cardiovascular disease; HR = hazard ratio.

analyses, which largely showed consistent results when we excluded participants with missing covariates (**Supplement Table 7**), removed the sugar added to coffee from total sugar and the energy it produced from total energy (**Supplement Table 8**), and accounted for environmental factors (**Supplement Table 10**). Results were slightly attenuated when we excluded participants who had an outcome event during the first 2 years of follow-up and when we excluded a coffee measurement if a participant reported having an unusual coffee consumption day. After excluding participants who were drinking coffee the year prior but not drinking coffee the day before, the inverse associations were slightly strengthened. The E-values (**Supplement Table 11**, available at Annals.org) of unsweetened, sugar-sweetened, and artificially sweetened coffee consumers ranged from 1.67 (SD, 1.29) to 2.26 (SD, 1.67).

Discussion

In this prospective, population-based cohort of 171 616 persons without prior CVD or cancer events, we found that moderate consumption of unsweetened coffee and that of sugar-sweetened coffee were associated with similar reductions in risk for death. However, the associations for artificially sweetened coffee intake were less consistent and conclusive across outcomes because of imprecise estimates. For instant, ground, and decaffeinated coffee, the results were consistent with our primary results. These associations were independent of measures of potential confounders, including sociodemographic factors, lifestyle behaviors, comorbid conditions, and environmental factors.

The current findings were consistent with findings from previous meta-analyses of observational studies (2, 3, 22) that moderate coffee consumption was associated with a U-shaped low risk for all-cause mortality. In contrast to our findings, Mendelian randomization studies showed that genetically predicted high coffee consumption was not associated with all-cause or CVD mortality (23–25), which means that coffee consumption does not have considerable health effects and that most of the observed associations between coffee consumption

Table 2. Associations of Coffee Consumption With All-Cause and Cause-Specific Mortality

Outcome	Nonconsumers	Coffee Consumers*				
		>0–1.5 Drinks/d	>1.5–2.5 Drinks/d	>2.5–3.5 Drinks/d	>3.5–4.5 Drinks/d	>4.5 Drinks/d
Unsweetened coffee (*n* = 136 619)						
All-cause mortality						
Events, *n (%)*	791 (1.9)	378 (1.6)	463 (1.7)	302 (1.5)	197 (1.6)	211 (1.9)
Basic model†	1 (Reference)	0.72 (0.64–0.81)	0.78 (0.70–0.88)	0.70 (0.61–0.80)	0.74 (0.63–0.87)	0.89 (0.77–1.04)
Multivariable model‡	1 (Reference)	0.79 (0.70–0.90)	0.84 (0.74–0.95)	0.71 (0.62–0.82)	0.71 (0.60–0.84)	0.77 (0.65–0.91)
Cancer mortality						
Events, *n (%)*	423 (1.0)	199 (0.8)	277 (1.0)	157 (0.8)	108 (0.9)	120 (1.1)
Basic model†	1 (Reference)	0.70 (0.59–0.83)	0.87 (0.75–1.01)	0.68 (0.56–0.81)	0.76 (0.62–0.94)	0.95 (0.78–1.16)
Multivariable model‡	1 (Reference)	0.77 (0.65–0.91)	0.93 (0.79–1.09)	0.69 (0.57–0.84)	0.73 (0.59–0.92)	0.83 (0.67–1.04)
CVD mortality						
Events, *n (%)*	151 (0.4)	74 (0.3)	84 (0.3)	58 (0.3)	44 (0.4)	36 (0.3)
Basic model†	1 (Reference)	0.74 (0.56–0.97)	0.74 (0.56–0.96)	0.69 (0.51–0.94)	0.86 (0.62–1.21)	0.79 (0.55–1.14)
Multivariable model‡	1 (Reference)	0.79 (0.60–1.05)	0.76 (0.57–1.00)	0.66 (0.48–0.91)	0.75 (0.53–1.08)	0.62 (0.42–0.91)
Sugar-sweetened coffee (*n* = 66 091)						
All-cause mortality						
Events, *n (%)*	791 (1.9)	192 (2.2)	127 (1.8)	83 (2.0)	56 (2.3)	81 (3.6)
Basic model†	1 (Reference)	0.90 (0.77–1.06)	0.72 (0.59–0.86)	0.82 (0.65–1.02)	0.96 (0.73–1.25)	1.58 (1.25–1.98)
Multivariable model‡	1 (Reference)	0.91 (0.78–1.07)	0.69 (0.57–0.84)	0.72 (0.57–0.91)	0.79 (0.60–1.06)	1.05 (0.82–1.36)
Cancer mortality						
Events, *n (%)*	423 (1.0)	108 (1.3)	63 (0.9)	45 (1.1)	35 (1.5)	49 (2.2)
Basic model†	1 (Reference)	0.98 (0.79–1.21)	0.69 (0.53–0.90)	0.86 (0.63–1.17)	1.17 (0.82–1.65)	1.87 (1.39–2.52)
Multivariable model‡	1 (Reference)	0.95 (0.76–1.18)	0.62 (0.47–0.82)	0.71 (0.51–0.98)	0.90 (0.62–1.30)	1.14 (0.82–1.60)
CVD mortality						
Events, *n (%)*	151 (0.4)	32 (0.4)	28 (0.4)	17 (0.4)	10 (0.4)	14 (0.6)
Basic model†	1 (Reference)	0.74 (0.51–1.09)	0.77 (0.52–1.16)	0.82 (0.49–1.35)	0.83 (0.44–1.58)	1.33 (0.77–2.31)
Multivariable model‡	1 (Reference)	0.78 (0.53–1.16)	0.77 (0.51–1.18)	0.75 (0.44–1.28)	0.72 (0.37–1.41)	0.90 (0.49–1.65)
Artificially sweetened coffee (*n* = 51 874)						
All-cause mortality						
Events, *n (%)*	791 (1.9)	77 (2.9)	77 (2.8)	58 (2.8)	34 (2.4)	50 (3.4)
Basic model†	1 (Reference)	1.16 (0.92–1.47)	1.18 (0.93–1.49)	1.17 (0.90–1.53)	0.95 (0.68–1.34)	1.47 (1.11–1.96)
Multivariable model‡	1 (Reference)	0.95 (0.75–1.21)	0.94 (0.73–1.19)	0.88 (0.67–1.16)	0.65 (0.45–0.92)	0.89 (0.65–1.20)
Cancer mortality						
Events, *n (%)*	423 (1.0)	40 (1.5)	37 (1.4)	26 (1.3)	14 (1.0)	24 (1.6)
Basic model†	1 (Reference)	1.13 (0.82–1.57)	1.06 (0.76–1.49)	0.99 (0.67–1.47)	0.74 (0.44–1.27)	1.34 (0.89–2.02)
Multivariable model‡	1 (Reference)	0.97 (0.70–1.35)	0.87 (0.61–1.23)	0.76 (0.50–1.15)	0.51 (0.30–0.89)	0.84 (0.54–1.30)
CVD mortality						
Events, *n (%)*	151 (0.4)	23 (0.9)	15 (0.6)	17 (0.8)	12 (0.8)	13 (0.9)
Basic model†	1 (Reference)	1.75 (1.12–2.71)	1.15 (0.68–1.96)	1.72 (1.04–2.85)	1.68 (0.93–3.02)	1.93 (1.09–3.40)
Multivariable model‡	1 (Reference)	1.32 (0.84–2.07)	0.88 (0.51–1.52)	1.24 (0.73–2.10)	1.06 (0.57–1.98)	1.07 (0.58–1.96)

CVD = cardiovascular disease.
* 1 drink is equal to approximately 250 mL.
† Estimates are hazard ratios (95% CIs) from Cox regression models adjusted for age (continuous) and sex.
‡ Estimates are hazard ratios (95% CIs) from multivariable Cox regression models additionally adjusted for Townsend deprivation index (continuous), education level (degree or no degree), ethnicity (White or other), smoking status (current, former, or never), pack-years of smoking (continuous), physical activity level (low, moderate, or high), body mass index (continuous), waist circumference (continuous), hypertension (yes or no), diabetes (yes or no), depression (yes or no), family history of CVD (yes or no), family history of cancer (yes or no), long-standing illness (yes or no), cholesterol-lowering drug use (yes or no), blood pressure drug use (yes or no), vitamin and mineral supplement use (yes or no [vitamin A, B, C, D, or E; folic acid; or multivitamins/minerals]), and intake of total energy, total sugar, fresh fruit, vegetables, red meat, processed meat, alcohol, tea, milk, sugar-sweetened beverages, and artificially sweetened beverages.

and mortality may be due to confounding or reverse causation. Moderate coffee consumption may be an indicator of a normal and healthy lifestyle, as suggested elsewhere (24, 26); associations could be heavily confounded by lifestyle behavior. Nevertheless, Mendelian randomization studies on coffee consumption are also prone to bias, and the results of genetic studies should be interpreted in light of the observational results.

Of note, many of the observed associations (including our findings) between high coffee consumption and morbidity and mortality are present with caffeinated as well as decaffeinated coffee, and thus it seems unlikely that caffeine alone can explain all potential health effects of coffee (3). Coffee is a complex mixture, and several biological mechanisms have been examined to explain both the beneficial and the harmful effects of coffee intake on risk for death. It has been proposed that potential beneficial effects are seen mostly with moderate coffee intake, whereas harmful effects increase with high intake, which produces the observed U-shaped association with mortality (22, 27–29). Previous studies have shown that intake of SSBs and ASBs may contribute to risk for death by inducing cardiometabolic and chronic

Table 3. Associations of Coffee Consumption With All-Cause Mortality, by Type of Coffee

Type of Coffee	Nonconsumers	Coffee Consumers*				
		>0–1.5 Drinks/d	>1.5–2.5 Drinks/d	>2.5–3.5 Drinks/d	>3.5–4.5 Drinks/d	>4.5 Drinks/d
Unsweetened coffee†						
Instant (*n* = 107 862)	1 (Reference)	0.86 (0.74–1.00)	0.86 (0.75–0.99)	0.74 (0.64–0.86)	0.71 (0.59–0.85)	0.81 (0.68–0.96)
Ground (*n* = 97 772)	1 (Reference)	0.69 (0.57–0.82)	0.80 (0.69–0.93)	0.68 (0.57–0.81)	0.66 (0.54–0.81)	0.67 (0.55–0.82)
Decaffeinated (*n* = 58 733)	1 (Reference)	0.95 (0.75–1.19)	0.89 (0.71–1.11)	0.61 (0.45–0.82)	0.66 (0.46–0.95)	0.98 (0.73–1.32)
Sugar-sweetened coffee†						
Instant (*n* = 59832)	1 (Reference)	0.89 (0.73–1.08)	0.69 (0.56–0.86)	0.67 (0.52–0.88)	0.84 (0.63–1.13)	0.98 (0.75–1.29)
Ground (*n* = 52 828)	1 (Reference)	0.93 (0.73–1.20)	0.71 (0.54–0.94)	0.66 (0.46–0.93)	0.74 (0.49–1.11)	1.02 (0.72–1.44)
Decaffeinated (*n* = 44 885)	1 (Reference)	0.79 (0.53–1.19)	0.62 (0.37–1.01)	0.70 (0.38–1.27)	0.85 (0.40–1.80)	0.90 (0.44–1.83)
Artificially sweetened coffee†						
Instant (*n* = 50 111)	1 (Reference)	1.00 (0.76–1.30)	0.98 (0.76–1.27)	0.94 (0.71–1.25)	0.66 (0.46–0.96)	0.94 (0.69–1.28)
Ground (*n* = 45 594)	1 (Reference)	0.84 (0.53–1.35)	0.83 (0.55–1.25)	0.94 (0.63–1.42)	0.51 (0.27–0.95)	0.71 (0.45–1.11)
Decaffeinated (*n* = 43 807)	1 (Reference)	0.77 (0.45–1.31)	1.11 (0.71–1.75)	0.85 (0.48–1.51)	0.52 (0.23–1.17)	1.26 (0.75–2.09)

* 1 drink is equal to approximately 250 mL.
† Estimates are hazard ratios (95% CIs) from multivariable Cox regression models adjusted for age (continuous), sex, Townsend deprivation index (continuous), education level (degree or no degree), ethnicity (White or other), smoking status (current, former, or never), pack-years of smoking (continuous), physical activity level (low, moderate, or high), body mass index (continuous), waist circumference (continuous), hypertension (yes or no), diabetes (yes or no), depression (yes or no), family history of cardiovascular disease (yes or no), family history of cancer (yes or no), long-standing illness (yes or no), cholesterol-lowering drug use (yes or no), blood pressure drug use (yes or no), vitamin and mineral supplement use (yes or no [vitamin A, B, C, D, or E; folic acid; or multivitamins/minerals]), and intake of total energy, total sugar, fresh fruit, vegetables, red meat, processed meat, alcohol, tea, milk, sugar-sweetened beverages, and artificially sweetened beverages.

disease risk (13, 30–32); thus, sugar or sweeteners added to coffee may have harmful effects and should be used cautiously. Instead, unsweetened coffee can be consumed, and healthy creamer alternatives for coffee are suitable. However, it is important to consider how availability of and access to healthier alternative options vary among communities.

This study has several strengths, including its prospective design, large sample size, and wide range of coffee consumption information. Detailed data allowed us to include coffee that was not typically examined in other studies, including sugar-sweetened, artificially sweetened, and unsweetened coffee.

Our study has several potential limitations. First, given the observational nature of the studies, the possibility of residual confounding cannot be excluded. Second, the UK Biobank is not representative of the sampling population, and evidence exists of a "healthy volunteer" selection bias. However, valid assessments of exposure–disease relationships do not require a representative population (33). Third, misclassification of coffee consumption and physical activity is possible. Participants may misunderstand the volume of their typical drink in milliliters. Baseline exposure might not capture changes over time. People who are unhealthy at baseline (for example, those who have chronic diseases) may switch from sugar-sweetened to artificially sweetened or unsweetened coffee. Diet is a time-varying exposure, with individual dietary habits and food composition changing over time. Error in the measurement of dietary intake is a serious problem in epidemiologic studies because it can hamper the identification of associations between dietary factors and disease occurrence. Therefore, the ability of epidemiologic studies to detect the effects of small and highly variable dietary components is limited. Although the refinement of dietary assessment methods to reduce measurement errors is ongoing (for example, collecting multiple 24-hour recall surveys), measurement error is unlikely to ever be entirely eliminated from dietary assessment (34, 35). Fourth, the consumption of artificially sweetened coffee was much lower than that of unsweetened and sugar-sweetened coffee, diminishing the power to detect any association. The results associated with artificial sweeteners are likely to be subject to confounding by indication and may not be as useful or valid. Fifth, because of a short follow-up time, we observed relatively few incidences of death from specific causes, and we could not reliably test whether some associations were specific among certain causes of mortality.

In conclusion, this prospective analysis found that moderate consumption of unsweetened coffee and that of sugar-sweetened coffee were associated with similar reductions in risk for all-cause, cancer-related, and CVD-related mortality. These novel findings are of clinical and public health relevance.

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References

1. **Grosso G, Micek A, Godos J, et al.** Coffee consumption and risk of all-cause, cardiovascular, and cancer mortality in smokers and non-smokers: a dose-response meta-analysis. Eur J Epidemiol. 2016; 31:1191-1205. [PMID: 27699514] doi:10.1007/s10654-016-0202-2
2. **Kim Y, Je Y, Giovannucci E.** Coffee consumption and all-cause and cause-specific mortality: a meta-analysis by potential modifiers. Eur J Epidemiol. 2019;34:731-752. [PMID: 31055709] doi:10.1007/s10654-019-00524-3
3. **Poole R, Kennedy OJ, Roderick P, et al.** Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ. 2017;359:j5024. [PMID: 29167102] doi:10.1136/bmj.j5024
4. **Gunter MJ, Murphy N, Cross AJ, et al.** Coffee drinking and mortality in 10 European countries: a multinational cohort study. Ann Intern Med. 2017;167:236-247. [PMID: 28693038] doi:10.7326/M16-2945
5. **Loftfield E, Cornelis MC, Caporaso N, et al.** Association of coffee drinking with mortality by genetic variation in caffeine metabolism: findings from the UK Biobank. JAMA Intern Med. 2018;178:1086-1097. [PMID: 29971434] doi:10.1001/jamainternmed.2018.2425
6. **de Koning L, Malik VS, Kellogg MD, et al.** Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. Circulation. 2012;125:1735-41, S1. [PMID: 22412070] doi:10.1161/CIRCULATIONAHA.111.067017
7. **Fung TT, Malik V, Rexrode KM, et al.** Sweetened beverage consumption and risk of coronary heart disease in women. Am J Clin Nutr. 2009;89:1037-42. [PMID: 19211821] doi:10.3945/ajcn.2008.27140
8. **Pase MP, Himali JJ, Beiser AS, et al.** Sugar- and artificially sweetened beverages and the risks of incident stroke and dementia: a prospective cohort study. Stroke. 2017;48:1139-1146. [PMID: 28428346] doi:10.1161/STROKEAHA.116.016027
9. **Walker ME, Xanthakis V, Moore LL, et al.** Cumulative sugar-sweetened beverage consumption is associated with higher concentrations of circulating ceramides in the Framingham Offspring Cohort. Am J Clin Nutr. 2020;111:420-428. [PMID: 31826243] doi:10.1093/ajcn/nqz257
10. **Bernstein AM, de Koning L, Flint AJ, et al.** Soda consumption and the risk of stroke in men and women. Am J Clin Nutr. 2012;95:1190-9. [PMID: 22492378] doi:10.3945/ajcn.111.030205
11. **Eshak ES, Iso H, Kokubo Y, et al.** Soft drink intake in relation to incident ischemic heart disease, stroke, and stroke subtypes in Japanese men and women: the Japan Public Health Centre-based study cohort I. Am J Clin Nutr. 2012;96:1390-7. [PMID: 23076619] doi:10.3945/ajcn.112.037903
12. **Mullee A, Romaguera D, Pearson-Stuttard J, et al.** Association between soft drink consumption and mortality in 10 European countries. JAMA Intern Med. 2019;179:1479-1490. [PMID: 31479109] doi:10.1001/jamainternmed.2019.2478
13. **Malik VS, Li Y, Pan A, et al.** Long-term consumption of sugar-sweetened and artificially sweetened beverages and risk of mortality in US adults. Circulation. 2019;139:2113-2125. [PMID: 30882235] doi:10.1161/CIRCULATIONAHA.118.037401
14. **Bechthold A, Boeing H, Schwedhelm C, et al.** Food groups and risk of coronary heart disease, stroke and heart failure: a systematic review and dose-response meta-analysis of prospective studies. Crit Rev Food Sci Nutr. 2019;59:1071-1090. [PMID: 29039970] doi:10.1080/10408398.2017.1392288
15. **Narain A, Kwok CS, Mamas MA.** Soft drinks and sweetened beverages and the risk of cardiovascular disease and mortality: a systematic review and meta-analysis. Int J Clin Pract. 2016;70:791-805. [PMID: 27456347] doi:10.1111/ijcp.12841
16. **Palmer LJ.** UK Biobank: bank on it. Lancet. 2007;369:1980-1982. [PMID: 17574079] doi:10.1016/S0140-6736(07)60924-6
17. **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:e1001779. [PMID: 25826379] doi:10.1371/journal.pmed.1001779
18. **Liu B, Young H, Crowe FL, et al.** Development and evaluation of the Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h dietary intakes in large-scale prospective studies. Public Health Nutr. 2011;14:1998-2005. [PMID: 21729481] doi:10.1017/S1368980011000942
19. **UK Biobank.** Mortality data: linkage to death registries. June 2020. Accessed at https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/DeathLinkage.pdf on 23 February 2021.
20. **Okely AD, Kontsevaya A, Ng J, et al.** 2020 WHO guidelines on physical activity and sedentary behavior. Sports Med Health Sci. 2021;3:115-8. doi:10.1016/j.smhs.2021.05.001
21. **VanderWeele TJ, Ding P.** Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med. 2017;167:268-274. [PMID: 28693043] doi:10.7326/M16-2607
22. **Ding M, Bhupathiraju SN, Satija A, et al.** Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. Circulation. 2014;129:643-59. [PMID: 24201300] doi:10.1161/CIRCULATIONAHA.113.005925
23. **Ong JS, Law MH, An J, et al.** Association between coffee consumption and overall risk of being diagnosed with or dying from cancer among >300 000 UK Biobank participants in a large-scale Mendelian randomization study. Int J Epidemiol. 2019;48:1447-1456. [PMID: 31412118] doi:10.1093/ije/dyz144
24. **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;45:1938-1952. [PMID: 28031317] doi:10.1093/ije/dyw325
25. **Qian Y, Ye D, Huang H, et al.** Coffee consumption and risk of stroke: a Mendelian randomization study. Ann Neurol. 2020;87:525-532. [PMID: 32034791] doi:10.1002/ana.25693
26. **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;132:2305-15. [PMID: 26572796] doi:10.1161/CIRCULATIONAHA.115.017341

27. **Zhang Z, Hu G, Caballero B, et al.** Habitual coffee consumption and risk of hypertension: a systematic review and meta-analysis of prospective observational studies. Am J Clin Nutr. 2011;93:1212-9. [PMID: 21450934] doi:10.3945/ajcn.110.004044

28. **Verhoef P, Pasman WJ, Van Vliet T, et al.** Contribution of caffeine to the homocysteine-raising effect of coffee: a randomized controlled trial in humans. Am J Clin Nutr. 2002;76:1244-8. [PMID: 12450889]

29. **Urgert R, Katan MB.** The cholesterol-raising factor from coffee beans. Annu Rev Nutr. 1997;17:305-24. [PMID: 9240930]

30. **Rosinger A, Herrick K, Gahche J, et al.** Sugar-sweetened beverage consumption among U.S. adults, 2011-2014. NCHS Data Brief. 2017:1-8. [PMID: 28135185]

31. **Hirahatake KM, Jacobs DR, Shikany JM, et al.** Cumulative intake of artificially sweetened and sugar-sweetened beverages and risk of incident type 2 diabetes in young adults: the Coronary Artery Risk Development In Young Adults (CARDIA) Study. Am J Clin Nutr. 2019;110:733-741. [PMID: 31374564] doi:10.1093/ajcn/nqz154

32. **Collin LJ, Judd S, Safford M, et al.** Association of sugary beverage consumption with mortality risk in US adults: a secondary analysis of data from the REGARDS study. JAMA Netw Open. 2019;2:e193121. [PMID: 31099861] doi:10.1001/jamanetworkopen.2019.3121

33. **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;186:1026-1034. [PMID: 28641372] doi:10.1093/aje/kwx246

34. **Tarasuk VS, Brooker AS.** Interpreting epidemiologic studies of diet-disease relationships. J Nutr. 1997;127:1847-52. [PMID: 9278571]

35. **Satija A, Yu E, Willett WC, et al.** Understanding nutritional epidemiology and its role in policy. Adv Nutr. 2015;6:5-18. [PMID: 25593140] doi:10.3945/an.114.007492

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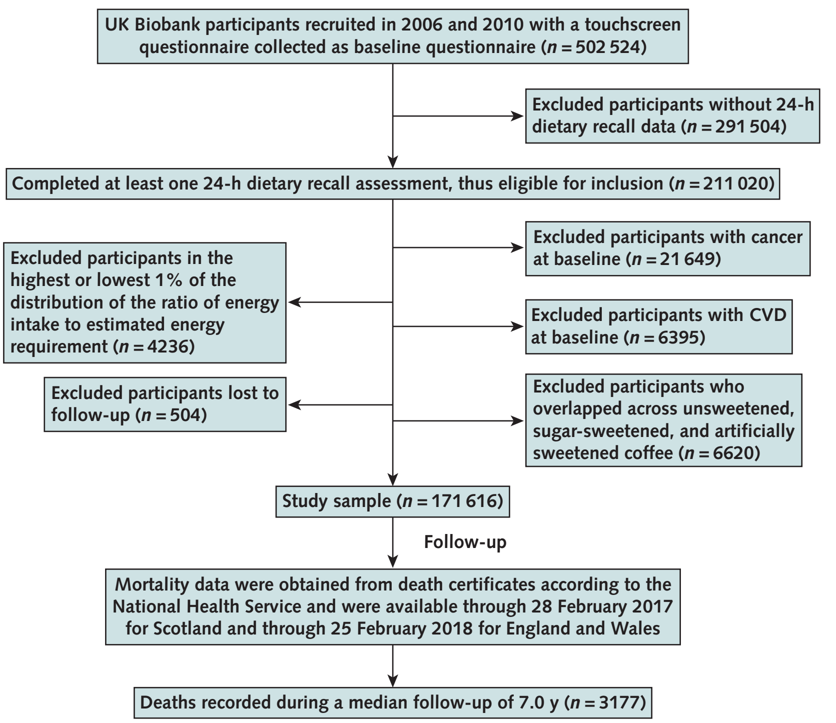
Appendix Figure. Study flow diagram.



CVD = cardiovascular disease.