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Association Between Caffeine Intake and All-Cause and Cause-Specific Mortality: A Population-Based Prospective Cohort Study

Tetsuro Tsujimoto, MD, PhD; Hiroshi Kajio, MD, PhD; and Takehiro Sugiyama, MD, MSHS, PhD

Abstract

Objective: To assess whether caffeine intake is associated with all-cause and cause-specific mortality.

Patients and Methods: We conducted a prospective cohort study using data from the National Health and Nutrition Examination Survey 1999-2010. Cox proportional hazards models were used to compare the multivariate-adjusted hazard ratios (HRs) of participants with a caffeine intake of 10 to 99, 100 to 199, and 200 mg/d or more with those of participants with a caffeine intake of less than 10 mg/d.

Results: In total, 17,594 participants were included, and the mean ± SD and median (interquartile range) follow-up was 6.5±2.8 years and 6.4 (3.6-9.5) years, respectively; 17,568 participants (99.8%) completed the follow-up, and 1310 died. Compared with those who had a caffeine intake of less than 10 mg/d, HRs and 95% CIs for all-cause mortality were significantly lower in participants with a caffeine intake of 10 to 99 mg/d (HR, 0.81; 95% CI, 0.66-1.00; P=.05), 100 to 199 mg/d (HR, 0.63; 95% CI, 0.51-0.78; P<.001), and 200 or more mg/d (HR, 0.69; 95% CI, 0.58-0.83; P<.001). A similar association was observed in participants who consumed less than 1 cup of coffee per week, and the HR was lowest in those with a caffeine intake of 100 to 199 mg/d (HR, 0.46; 95% CI, 0.22-0.93). There was no association between caffeine intake and cardiovascular mortality, whereas the HRs for noncardiovascular mortality were significantly lower in those with a caffeine intake of 10 to 99 mg/d (HR, 0.74; 95% CI, 0.57-0.95; P=.01), 100 to 199 mg/d (HR, 0.60; 95% CI, 0.46-0.77; P<.001), and 200 or more mg/d (HR, 0.65; 95% CI, 0.53-0.80; P<.001).

Conclusion: Moderate caffeine intake was associated with a decreased risk of all-cause mortality, regardless of the presence or absence of coffee consumption.

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From the Department of Diabetes, Endocrinology, and Metabolism, Center Hospital (T.T., H.K.), and Department of Clinical Study and Informatics, Center for Clinical Sciences (T.S.), National Center for Global Health and Medicine, Tokyo, Japan; and Department of Public Health/Health Policy, the University of Tokyo, Tokyo, Japan (T.S.).

Coffee is consumed worldwide. Many observational studies have reported a significant inverse association between coffee consumption and all-cause and cause-specific mortality,[1-4] including mortality due to cardiovascular disease,[1-4] respiratory disease,[1,2,4] infection,[1,2] neurologic disease,[3] and injuries and accidents.[1] In addition, a recent study suggested that higher coffee consumption may be associated with reduced cancer recurrence and death in patients with colon cancer.[5]

Caffeine is the most studied compound of coffee, and coffee consumption accounts for 71% of caffeine intake among adults in the United States.[6] Excessive caffeine intake can lead to an increase in sympathetic activity and circulating catecholamine concentrations mediated by stimulation of the central nervous system,[7] which could result in significant cardiovascular stress.[8] However, few studies have investigated the association between daily caffeine intake and mortality, and no study has yet evaluated the effects of caffeine intake compared with no caffeine intake. Therefore, the aim of this study was to assess whether caffeine intake is associated with all-cause and cause-specific mortality. In addition, the association between caffeine intake and mortality among participants who did not consume coffee was also investigated.

PATIENTS AND METHODS

Data Source and Study Population

We conducted a prospective cohort study using data from the US National Health and

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TABLE 1. Baseline Characteristics of the 17,594 Study Participants, Stratified by Daily Caffeine Intake[a,b,c]

Characteristic	Caffeine intake (mg/d)				*P* value for between-group comparison[d]	*P* value for trend[e]
	<10	10-99	100-199	≥200		
Unweighted sample	3943	4320	3745	5586		
Age (y)	48.1±14.8	48.2±13.5	49.4±11.7	50.4±9.7	<.001	<.001
Female sex	59.0	59.2	56.5	45.9	<.001	<.001
Race and ethnicity						
Non-Hispanic white	60.7	68.8	75.7	87.2	<.001	<.001
Non-Hispanic black	21.1	13.0	9.0	3.8	<.001	<.001
Mexican American	7.1	7.1	5.5	3.2	<.001	<.001
Other[f]	11.1	11.1	9.8	5.8	<.001	<.001
Education						
Less than high school	17.0	15.2	15.2	13.2	<.001	<.001
High school or GED	21.3	23.7	22.4	24.4	.04	.03
More than high school	61.7	61.1	62.4	62.4	.69	.42
Smoking status						
Never	65.4	61.8	54.4	39.0	<.001	<.001
Former	22.3	23.5	28.6	33.7	<.001	<.001
Current	12.3	14.7	17.0	27.3	<.001	<.001
Body mass index (kg/m^2)	29.4±6.6	28.9±5.8	28.9±5.4	28.8±4.7	.04	.03
<18.5	1.8	1.2	1.3	1.0	.05	.01
18.5-24.9	27.8	28.7	27.9	27.6	.87	.70
25.0-29.9	30.8	33.1	33.3	36.7	<.001	<.001
30.0-34.9	20.5	21.5	22.1	20.2	.31	.59
≥35.0	19.1	15.5	15.4	14.5	<.001	.001
Dyslipidemia	37.4	39.2	41.1	40.9	.01	.002
Hypertension	37.8	34.8	34.5	33.2	.01	.004
Diabetes	13.7	11.7	11.6	10.4	.001	<.001
Macrovascular diseases						
Coronary heart disease	7.5	6.6	6.5	7.6	.25	.63
Heart failure	3.1	2.3	2.0	2.4	.07	.17
Stroke	3.1	3.0	2.5	2.5	.24	.06
Cancer	9.9	9.6	10.5	10.2	.75	.49
Nutrition						
Total energy (kcal)	1947±833	2072±806	2096±750	2291±735	<.001	<.001
Total carbohydrate (g)	242±111	258±106	255±97	268±96	<.001	<.001
Total protein (g)	71±38	78±38	79±35	90±36	<.001	<.001
Total fat (g)	78±37	80±35	80±31	88±31	<.001	<.001

[a]GED = general educational development.
[b]Following the Centers for Disease Control and Prevention's recommendations for the analysis of NHANES data, we used an appropriate weight for each analysis, based on the variables selected. The weights were provided by the National Center for Health Statistics and accounted for unequal probabilities of selection and non-responses to make unbiased national estimates.
[c]Data are presented as No. (percentage) of participants or mean ± SD.
[d]*P* value was calculated with analysis of variance for continuous variables and χ^2 tests for categorical variables.
[e]Linear trends across categories of caffeine intake were assessed with linear regression for continuous variables and χ^2 tests for categorical variables.
[f]The category includes other Hispanics and other races including multiracial participants.

Nutrition Examination Survey (NHANES).[9] Written informed consent was obtained from all participants. The National Center for Health Statistics (NCHS) Research Ethics Review Board approved the NHANES protocols.[10] The NHANES was conducted by the NCHS at the Centers for Disease Control and Prevention and employed a stratified, multistage probability sampling design to enable representation of the US civilian noninstitutionalized population.[9] In this study, data were collected at home and mobile examination centers (MECs). To assess the health and nutritional status of adults and children in the United States, blood specimens were collected during examinations at the MECs.

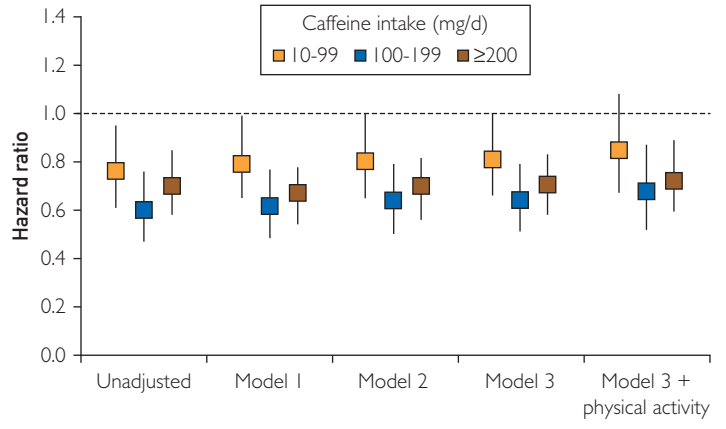

FIGURE 1. Hazard ratios for all-cause mortality according to daily caffeine intake. The reference line at 1.0 corresponds to the reference group with a caffeine intake of less than 10 mg/d.

Among the population participating in the NHANES during the period 1999-2010, the unweighted response rate of household interviews was 80.6% and that of the MEC examinations was 77.1%.[11] We focused on participants aged 20 to 79 years on the date of home interview (survey participation), which resulted in a sample of 29,725 participants. We excluded those with missing information on caffeine intake (n = 2700). In addition, those with missing information on any other potential confounders of this study were also excluded (n = 9431), which resulted in a final sample of 17,594. The study participants were prospectively followed-up from the date of survey participation until December 31, 2011.

Nutrition and Caffeine Intake

All NHANES participants were eligible for a 24-hour dietary recall interview. Dietary intake data were used to estimate the type and amount of foods and beverages consumed during the 24-hour period before the interview and to estimate the daily total intake of energy, nutrients, and other components from those foods and beverages. Although the NHANES 2003-2010 data set included 2-day dietary information, only the first dietary recall interview data were used to preserve comparability. All dietary recall interviews were conducted in person during examinations at the MECs. To help the respondent report the volume and dimensions of the food items consumed, each MEC dietary interview room contained a standard set of measuring guides. Participants were given measuring cups, spoons, a ruler, and a food model booklet.[12] The dietary interview component was conducted as a partnership between the US Department of Agriculture (USDA) and the US Department of Health and Human Services. Interview data files were sent electronically from the field and were imported into Survey Net, a computer-assisted food coding and data management system developed by the USDA.[13] The USDA dietary data collection instrument, the Automated Multiple-Pass Method,[14] was designed to provide an efficient and accurate means of collecting intake data for large-scale national surveys. Sources of caffeine included coffee, tea, soda, energy drinks, and chocolate- and cocoa-containing products, in consideration of caffeinated and decaffeinated versions.[15] Total caffeine intake was calculated, and the amount of caffeine was divided into 4 groups (<10, 10-99, 100-199, and ≥200 mg/d; 1 cup of coffee contains approximately 100 mg of caffeine).

Outcome Measurements

The main outcome measure of this study was all-cause mortality. In addition, cardiovascular, noncardiovascular, and cancer mortality were evaluated. We used the mortality follow-up data provided in the Public-use Linked Mortality Files.[16] The Public-use Linked Mortality Files are available for NHANES for the period 1999-2010 and have been updated through December 31, 2011. We prospectively followed up study participants from the survey participation interview date until the date of death or until December 31, 2011. To identify the causes of death of study participants, the NHANES used the *International Classification of Diseases, Tenth Revision*, for deaths occurring in or after 1999. The specific codes used in this study were as follows: I00-I09, I11, I13, I20-I51, and I60-I69 for causes of death from cardiovascular disease (cardiovascular death) and C00-C97 for causes of death from malignant neoplasms (cancer death).[17] Follow-up was censored at the time of death from other causes.

Potential Confounders

We extracted data on potential confounders: age, sex, race and ethnicity, education, smoking status, and body mass index (BMI;

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calculated as weight in kilograms divided by height in meters squared), dyslipidemia, hypertension, diabetes, coronary heart disease, heart failure, stroke, cancer, and total daily intakes of energy, carbohydrate, fat, and protein. Race and ethnicity were classified into 4 categories: non-Hispanic white, non-Hispanic black, Mexican American, and others including other Hispanics, Asians, and multiracial participants. Education was classified

TABLE 2. Hazard Ratios for All-Cause Mortality of the 17,594 Study Participants, Stratified by Daily Caffeine Intake[a,b]

Variable	Caffeine (mg/d)				*P* value for trend[c]
	<10	10-99	100-199	≥200	
All participants	3943	4320	3745	5586	
Deaths from any cause	343	311	247	409	NA
Event rate (per 1000 person-years)	12.2	9.3	7.2	8.6	NA
Unadjusted HR	1.00 [ref]	**0.76 (0.61-0.95)**	**0.60 (0.47-0.76)**	**0.70 (0.58-0.85)**	.001
Multivariate-adjusted HR, model 1[d]	1.00 [ref]	**0.80 (0.65-0.99)**	**0.61 (0.48-0.77)**	**0.65 (0.54-0.78)**	<.001
Multivariate-adjusted HR, model 2[e]	1.00 [ref]	0.81 (0.65-1.00)	**0.63 (0.50-0.79)**	**0.68 (0.56-0.82)**	<.001
Multivariate-adjusted HR, model 3[f]	1.00 [ref]	0.81 (0.66-1.00)	**0.63 (0.51-0.78)**	**0.69 (0.58-0.83)**	<.001
Participants with obesity	1644	1724	1494	2097	
Deaths from any cause	133	111	95	150	NA
Event rate (per 1000 person-years)	13.4	9.6	7.8	9.5	NA
Unadjusted HR	1.00 [ref]	0.72 (0.51-1.00)	**0.58 (0.42-0.79)**	**0.70 (0.52-0.93)**	.02
Multivariate-adjusted HR, model 1	1.00 [ref]	0.78 (0.53-1.15)	**0.59 (0.41-0.83)**	**0.65 (0.46-0.90)**	.007
Multivariate-adjusted HR, model 2	1.00 [ref]	0.84 (0.58-1.21)	**0.63 (0.46-0.86)**	**0.69 (0.50-0.96)**	.01
Multivariate-adjusted HR, model 3	1.00 [ref]	0.85 (0.59-1.22)	**0.64 (0.47-0.88)**	**0.72 (0.52-0.99)**	.02
Participants with dyslipidemia	1550	1783	1653	2378	
Deaths from any cause	154	153	136	191	NA
Event rate (per 1000 person-years)	14.3	12.1	9.6	10.5	NA
Unadjusted HR	1.00 [ref]	0.85 (0.62-1.16)	**0.67 (0.50-0.89)**	**0.73 (0.56-0.95)**	.01
Multivariate-adjusted HR, model 1	1.00 [ref]	0.91 (0.66-1.26)	**0.70 (0.53-0.92)**	**0.71 (0.54-0.92)**	.006
Multivariate-adjusted HR, model 2	1.00 [ref]	0.90 (0.66-1.23)	**0.73 (0.55-0.97)**	**0.74 (0.57-0.97)**	.01
Multivariate-adjusted HR, model 3	1.00 [ref]	0.90 (0.66-1.24)	**0.75 (0.56-0.98)**	**0.75 (0.57-0.98)**	.02
Participants with hypertension	1672	1705	1496	2107	
Deaths from any cause	227	200	153	235	NA
Event rate (per 1000 person-years)	21.7	17.2	13.0	15.5	NA
Unadjusted HR	1.00 [ref]	0.79 (0.59-1.04)	**0.61 (0.46-0.78)**	**0.71 (0.56-0.90)**	.004
Multivariate-adjusted HR, model 1	1.00 [ref]	0.83 (0.64-1.09)	**0.63 (0.48-0.81)**	**0.71 (0.55-0.91)**	.003
Multivariate-adjusted HR, model 2	1.00 [ref]	0.83 (0.64-1.07)	**0.64 (0.51-0.79)**	**0.71 (0.56-0.91)**	.003
Multivariate-adjusted HR, model 3	1.00 [ref]	0.84 (0.64-1.08)	**0.64 (0.52-0.79)**	**0.72 (0.56-0.92)**	.003
Participants with diabetes	749	706	638	808	
Deaths from any cause	123	98	81	115	NA
Event rate (per 1000 person-years)	26.7	23.1	18.6	24.8	NA
Unadjusted HR	1.00 [ref]	0.86 (0.58-1.27)	0.70 (0.48-1.02)	0.93 (0.66-1.31)	.67
Multivariate-adjusted HR, model 1	1.00 [ref]	0.83 (0.56-1.21)	**0.67 (0.47-0.95)**	0.84 (0.59-1.18)	.29
Multivariate-adjusted HR, model 2	1.00 [ref]	0.90 (0.62-1.30)	0.78 (0.55-1.12)	0.85 (0.61-1.18)	.28
Multivariate-adjusted HR, model 3	1.00 [ref]	0.90 (0.62-1.30)	0.79 (0.55-1.11)	0.84 (0.60-1.17)	.26
Participants with CHD and/or HF	370	398	363	572	
Deaths from any cause	100	75	79	117	NA
Event rate (per 1000 person-years)	50.0	31.2	35.8	32.2	NA
Unadjusted HR	1.00 [ref]	**0.61 (0.42-0.87)**	0.71 (0.49-1.04)	**0.62 (0.43-0.89)**	.03
Multivariate-adjusted HR, model 1	1.00 [ref]	**0.60 (0.40-0.89)**	0.70 (0.48-1.01)	**0.69 (0.50-0.96)**	.08
Multivariate-adjusted HR, model 2	1.00 [ref]	**0.64 (0.43-0.96)**	0.73 (0.50-1.05)	**0.70 (0.50-0.98)**	.08
Multivariate-adjusted HR, model 3	1.00 [ref]	**0.63 (0.42-0.95)**	0.72 (0.49-1.05)	**0.72 (0.51-0.99)**	.11
Participants with cancer	349	389	371	624	
Deaths from any cause	71	63	62	101	NA
Event rate (per 1000 person-years)	36.9	23.1	19.0	26.2	NA

Continued on next page

TABLE 2. Continued

Variable	Caffeine (mg/d)				*P* value for trend[c]
	<10	10-99	100-199	≥200	
Participants with cancer, continued					
Unadjusted HR	1.00 [ref]	0.63 (0.37-1.05)	**0.51 (0.32-0.80)**	0.70 (0.47-1.05)	.18
Multivariate-adjusted HR, model 1	1.00 [ref]	0.64 (0.40-1.02)	**0.55 (0.35-0.87)**	0.71 (0.46-1.09)	.21
Multivariate-adjusted HR, model 2	1.00 [ref]	0.65 (0.40-1.06)	**0.57 (0.36-0.91)**	0.73 (0.49-1.10)	.20
Multivariate-adjusted HR, model 3	1.00 [ref]	0.66 (0.40-1.07)	**0.59 (0.37-0.93)**	0.72 (0.48-1.10)	.20

[a]CHD = coronary heart disease; HF = heart failure; HR = hazard ratio; NA = not applicable; ref = reference.

[b]Data are presented as number or hazard ratio (95% CI). Boldface type indicates a significant difference ($P<.05$).

[c]*P* values for linear trend were calculated by assigning scores for categories of caffeine intake, starting from 0 for a caffeine intake of 10 mg/d to 3 for the highest intake, used as a continuous variable.

[d]Multivariate model 1 included adjustments for potential confounders as follows: age, sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), education (less than high school, high school graduation or general education development certificate, and more than high school), current smoking status (current smoker, former smoker, and never smoked), and body mass index (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, and ≥35.0 kg/m^2).

[e]Multivariate model 2 included adjustments for the potential confounders of model 1 plus dyslipidemia, hypertension, diabetes, CHD, HF, stroke, and cancer.

[f]Multivariate model 3 included adjustments for the potential confounders of models 1 and 2 plus total daily intake of energy, carbohydrates, fat, and protein. Multivariate analyses limited to participants with obesity, dyslipidemia, hypertension, diabetes, CHD/HF, or cancer did not include the confounder body mass index, dyslipidemia, hypertension, diabetes, CHD/HF, or cancer, respectively.

as less than high school, more than high school, and high school graduation or general education development certificate. Smoking status was classified into 3 groups: current smoker, former smoker, and never smoked. The BMI was classified into 5 groups: less than 18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, and 35.0 kg/m^2 or more. Obesity was defined as a BMI of 30.0 kg/m^2 or more. Dyslipidemia was defined as a previous diagnosis of hyperlipidemia or intake of lipid-lowering medications. Hypertension was defined as either a previous diagnosis of hypertension or intake of antihypertensive medications. Diabetes was defined as a previous diagnosis of diabetes, use of antidiabetic medications or insulin, or a glycated hemoglobin (A_{1c}) level of 6.5% or higher (to convert to proportion of total hemoglobin, multiply by 0.01). Coronary heart disease was defined as a previous diagnosis of coronary heart disease, myocardial infarction, or angina pectoris. Heart failure was defined as a previous diagnosis of congestive heart failure. Cancer was defined as a previous diagnosis of cancer/malignancy.

Statistical Analyses

Demographic data are presented as number and percentage or mean ± SD. Descriptive statistics for patient characteristics were calculated with analysis of variance for continuous variables and χ^2 tests for categorical variables. Linear trends across categories of caffeine intake were assessed by linear regression for continuous variables and χ^2 tests for categorical variables. For the analyses of the mortality outcomes, multivariate Cox proportional hazards regression was performed, and hazard ratios (HRs) and 95% CIs in participants with caffeine intake of 10-99, 100-199, and 200 mg/d or more were compared with those with a caffeine intake of less than 10 mg/d. *P* values for linear trend were calculated by assigning scores for categories of caffeine intake, starting from 0 for a caffeine intake of less than 10 mg/d to 3 for the highest intake, used as a continuous variable.[2,4] The multivariate-adjusted HRs were also analyzed separately for men and women. Multivariate model 1 included adjustments for potential confounders as follows: age, sex, race and ethnicity, education, smoking status, and BMI. Multivariate model 2 included adjustments for the potential confounders of model 1 plus dyslipidemia, hypertension, diabetes, coronary heart disease, heart failure, stroke, and cancer. Multivariate model 3 included adjustments for the potential confounders of models 1 and 2 plus total daily intakes of energy, carbohydrate, fat, and protein. In addition, to minimize residual confounding, self-reported health conditions (5 categories: excellent, very good, good, fair, or poor) were adjusted for sensitivity analysis.

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TABLE 3. Hazard Ratios for Cardiovascular, Noncardiovascular, and Cancer Mortality in 17,594 Study Participants[a,b]

Variable	Caffeine (mg/d)				*P* value for trend[c]
	<10 (n=3943)	10-99 (n=4320)	100-199 (n=3745)	≥200 (n=5586)	
Cardiovascular mortality					
Deaths from any cause	70	72	63	98	NA
Event rate (per 1000 person-years)	2.2	2.3	1.6	1.9	NA
Unadjusted HR	1.00 [ref]	1.05 (0.66-1.67)	0.71 (0.45-1.12)	0.84 (0.55-1.26)	.22
Multivariate-adjusted HR, model 1[d]	1.00 [ref]	1.13 (0.69-1.84)	0.73 (0.46-1.16)	0.77 (0.50-1.18)	.08
Multivariate-adjusted HR, model 2[e]	1.00 [ref]	1.16 (0.73-1.85)	0.78 (0.49-1.24)	0.83 (0.54-1.25)	.15
Multivariate-adjusted HR, model 3[f]	1.00 [ref]	1.16 (0.73-1.84)	0.80 (0.51-1.27)	0.88 (0.58-1.33)	.29
Noncardiovascular mortality					
Deaths from any cause	271	237	184	309	NA
Event rate (per 1000 person-years)	9.9	6.9	5.7	6.7	NA
Unadjusted HR	1.00 [ref]	**0.70 (0.53-0.91)**	**0.57 (0.43-0.76)**	**0.67 (0.53-0.84)**	.002
Multivariate-adjusted HR, model 1	1.00 [ref]	**0.73 (0.57-0.94)**	**0.59 (0.44-0.77)**	**0.62 (0.50-0.78)**	<.001
Multivariate-adjusted HR, model 2	1.00 [ref]	**0.74 (0.58-0.95)**	**0.61 (0.46-0.79)**	**0.68 (0.55-0.84)**	.001
Multivariate-adjusted HR, model 3	1.00 [ref]	**0.74 (0.57-0.95)**	**0.60 (0.46-0.77)**	**0.65 (0.53-0.80)**	<.001
Cancer mortality					
Deaths from any cause	91	91	75	121	NA
Event rate (per 1000 person-years)	3.1	2.6	2.2	2.5	NA
Unadjusted HR	1.00 [ref]	0.82 (0.56-1.20)	0.72 (0.50-1.02)	0.79 (0.60-1.05)	.15
Multivariate-adjusted HR, model 1	1.00 [ref]	0.86 (0.57-1.29)	0.70 (0.47-1.04)	**0.68 (0.47-0.97)**	.02
Multivariate-adjusted HR, model 2	1.00 [ref]	0.84 (0.55-1.29)	0.68 (0.46-1.01)	**0.67 (0.48-0.96)**	.02
Multivariate-adjusted HR, model 3	1.00 [ref]	0.86 (0.56-1.31)	0.69 (0.47-1.04)	0.70 (0.50-1.00)	.04

[a]HR = hazard ratio; NA = not applicable; ref = reference.

[b]Data are presented as number or hazard ratio (95% CI). Boldface type indicates a significant difference ($P<.05$).

[c]*P* values for linear trend were calculated by assigning scores for categories of caffeine intake, starting from 0 for a caffeine intake of 10 mg/d to 3 for the highest intake, used as a continuous variable.

[d]Multivariate model 1 included adjustments for potential confounders as follows: age, sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), education (less than high school, high school graduation or general education development certificate, and more than high school), current smoking status (current smoker, former smoker, and never smoked), and body mass index (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, and ≥35.0 kg/m^2).

[e]Multivariate model 2 included adjustments for the potential confounders of model 1 plus dyslipidemia, hypertension, diabetes, coronary heart disease, heart failure, stroke, and cancer.

[f]Multivariate model 3 included adjustments for the potential confounders of models 1 and 2 plus total daily intake of energy, carbohydrates, fat, and protein.

Furthermore, because the present study had missing information about caffeine intake and other potential confounders, we performed a sensitivity analysis for all-cause mortality using multiple imputation to handle missing data. To impute missing values, we used an iterative Markov chain Monte Carlo method, which filled in missing values of one or more variables using multivariate regression.[18] We constructed models, including all variables in Table 1 that were potentially related to the missing values and outcomes, and analyzed 20 multiply imputed data sets.

Although the NHANES measured physical activity, this variable was not included in the main analyses owing to inconsistent measurements, which changed between the 2005-2006 and 2007-2008 periods. Therefore, as another sensitivity analysis, physical activity in the NHANES 1999-2006 period was added as an adjustment to model 3. Physical activity was divided into 2 groups according to a cutoff value of 150 min/wk of walking and/or bicycling.[19,20] Furthermore, other sensitivity analyses were performed using the coffee intake data collected in the NHANES period 2003-2006. To exclude the potential effects of coffee components other than caffeine, the association between caffeine intake and mortality was validated in the participants who consumed less than 1 cup of coffee per week. Furthermore, the total amount of caffeine was assessed according to the number of cups of coffee or decaffeinated coffee.

All statistical analyses were conducted using Stata statistical software, version 14.1

TABLE 4. Hazard Ratios for Cardiovascular, Noncardiovascular, and Cancer Mortality After Multivariate Adjustment With Physical Activity[a,b]

Variable	Caffeine (mg/d)				*P* value for trend[c]
	<10 (n=2375)	10-99 (n=2476)	100-199 (n=2139)	≥200 (n=3330)	
Cardiovascular mortality					
Deaths from any cause	59	54	49	84	NA
Event rate (per 1000 person-years)	2.3	2.4	1.7	2.0	NA
Multivariate-adjusted HR[d]	1.00 [ref]	1.12 (0.67-1.88)	0.83 (0.49-1.42)	0.86 (0.53-1.39)	.34
Noncardiovascular mortality					
Deaths from any cause	210	189	146	246	NA
Event rate (per 1000 person-years)	10.1	7.5	6.0	7.0	NA
Multivariate-adjusted HR	1.00 [ref]	0.78 (0.58-1.05)	**0.64 (0.48-0.87)**	**0.69 (0.54-0.88)**	.004
Cancer mortality					
Deaths from any cause	73	74	65	93	NA
Event rate (per 1000 person-years)	3.2	2.9	2.5	2.6	NA
Multivariate-adjusted HR	1.00 [ref]	0.88 (0.54-1.44)	0.74 (0.48-1.16)	0.74 (0.50-1.09)	.11

[a]HR = hazard ratio; NA = not applicable; ref = reference.

[b]Data are presented as number or hazard ratio (95% CI). Boldface type indicates a significant difference (*P*<.05).

[c]*P* values for linear trend were calculated by assigning scores for categories of caffeine intake, starting from 0 for a caffeine intake of 10 mg/d to 3 for the highest intake, used as a continuous variable.

[d]Multivariate model included adjustments for potential confounders as follows: age, sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), education (less than high school, high school graduation or general education development certificate, and more than high school), current smoking status (current smoker, former smoker, and never smoked), and body mass index (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, and ≥35.0 kg/m^2), dyslipidemia, hypertension, diabetes, coronary heart disease, heart failure, stroke, cancer, total daily intake of energy, carbohydrate, fat, and protein, and physical activity.

(StataCorp), accounting for the complex survey design. Following the Centers for Disease Control and Prevention's recommendations for the analysis of NHANES data, we used an appropriate weight for each analysis, based on the variables selected. The weights were provided by the NCHS and accounted for unequal probabilities of selection and nonresponses to make unbiased national estimates. *P*<.05 was considered statistically significant for all tests.

RESULTS

The characteristics of all study participants aged 20 to 79 years are presented in Table 1. Among the 17,594 study participants, 3943 (22.4%) had a caffeine intake of less than 10 mg/d, 4320 (24.6%) consumed 10 to 99 mg/d, 3745 (21.3%) consumed 100 to 199 mg/d, and 5586 (31.7%) consumed 200 mg/d or more. Of the 17,594 study participants, 12,008 (68.3%) had a caffeine intake of less than 200 mg/d. Participants with higher caffeine intakes were associated with older age, more proportion of male sex and non-Hispanic white, less proportion of education attainment of less than high school, more smoking, lower proportion of BMI of ≥35.0 kg/m^2, higher prevalence of dyslipidemia, lower prevalence of diabetes and hypertension, and higher daily intakes of total energy, carbohydrate, protein, and fat, with *P* values of <.05 for trends across all categories. Conversely, caffeine intake was not associated with a history of macrovascular diseases or cancer.

The HRs for all-cause mortality according to daily caffeine intake are shown in Figure 1. The mean ± SD and median (interquartile range) follow-up periods were 6.5±2.8 and 6.4 (3.6-9.5) years, respectively. Of the total study population, 17,568 (99.8%) completed the follow-up, and a total of 1310 deaths were reported. Compared with those with a caffeine intake of less than 10 mg/d, unadjusted HRs (95% CIs) for all-cause mortality were significantly lower in the participants with a caffeine intake of 10 to 99 mg/d (HR, 0.76; 95% CI, 0.61-0.95; *P*=.01), 100 to 199 mg/d (HR, 0.60; 95% CI, 0.47-0.76; *P*<.001), and 200 mg/d or more (HR, 0.70; 95% CI, 0.58-0.85; *P*<.001). The same inverse associations were observed after multivariate adjustment. Compared with participants with a caffeine intake of <10 mg/day, HRs for all-cause mortality in multivariate model 3 were significantly lower in those with a caffeine intake of 10-99 mg/day (HR, 0.81; 95% CI, 0.66-1.00; *P*=.05), 100-199 mg/day (HR, 0.63; 95% CI,

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TABLE 5. Hazard Ratios for All-Cause, Cardiovascular, and Noncardiovascular Mortality in Men and Women[a,b]

Variable	Caffeine (mg/d)				*P* value for trend[c]
	<10	10-99	100-199	≥200	
Men	1576	1772	1716	3106	NA
All-cause mortality					
Deaths from any cause	181	177	144	279	NA
Event rate (per 1000 person-years)	13.4	11.4	8.9	10.6	NA
Unadjusted HR	1.00 [ref]	0.84 (0.62-1.13)	**0.66 (0.49-0.89)**	0.78 (0.59-1.02)	.07
Multivariate-adjusted HR, model 1[d]	1.00 [ref]	0.89 (0.65-1.20)	**0.68 (0.51-0.91)**	0.74 (0.55-1.01)	.03
Multivariate-adjusted HR, model 2[e]	1.00 [ref]	0.89 (0.65-1.20)	**0.71 (0.54-0.94)**	0.78 (0.58-1.04)	.07
Multivariate-adjusted HR, model 3[f]	1.00 [ref]	0.90 (0.66-1.21)	**0.71 (0.54-0.94)**	0.79 (0.59-1.05)	.07
Cardiovascular mortality					
Deaths from any cause	40	45	40	78	NA
Event rate (per 1000 person-years)	2.6	3.4	2.3	2.6	NA
Unadjusted HR	1.00 [ref]	1.31 (0.66-2.60)	0.89 (0.42-1.87)	0.98 (0.51-1.89)	.59
Multivariate-adjusted HR, model 1	1.00 [ref]	1.47 (0.75-2.87)	0.95 (0.46-1.96)	1.03 (0.52-2.00)	.62
Multivariate-adjusted HR, model 2	1.00 [ref]	1.51 (0.79-2.89)	1.03 (0.50-2.12)	1.10 (0.58-2.09)	.80
Multivariate-adjusted HR, model 3	1.00 [ref]	1.49 (0.77-2.89)	1.03 (0.49-2.14)	1.15 (0.60-2.23)	.96
Noncardiovascular mortality					
Deaths from any cause	139	130	104	201	NA
Event rate (per 1000 person-years)	10.8	7.9	6.7	8.1	NA
Unadjusted HR	1.00 [ref]	0.72 (0.51-1.02)	**0.61 (0.46-0.82)**	**0.74 (0.54-0.99)**	.09
Multivariate-adjusted HR, model 1	1.00 [ref]	0.75 (0.52-1.07)	**0.62 (0.46-0.85)**	**0.68 (0.47-0.98)**	.04
Multivariate-adjusted HR, model 2	1.00 [ref]	0.73 (0.51-1.06)	**0.63 (0.47-0.85)**	**0.70 (0.50-0.99)**	.05
Multivariate-adjusted HR, model 3	1.00 [ref]	0.75 (0.52-1.08)	**0.64 (0.48-0.85)**	**0.70 (0.50-0.99)**	.05
Cancer mortality					
Deaths from any cause	53	53	48	81	NA
Event rate (per 1000 person-years)	4.1	3.4	2.9	3.1	NA
Unadjusted HR	1.00 [ref]	0.83 (0.49-1.40)	0.71 (0.44-1.14)	0.75 (0.48-1.18)	.23
Multivariate-adjusted HR, model 1	1.00 [ref]	0.85 (0.48-1.50)	0.72 (0.42-1.22)	0.68 (0.39-1.18)	.15
Multivariate-adjusted HR, model 2	1.00 [ref]	0.83 (0.47-1.50)	0.72 (0.42-1.22)	0.68 (0.40-1.17)	.15
Multivariate-adjusted HR, model 3	1.00 [ref]	0.85 (0.47-1.54)	0.74 (0.43-1.26)	0.72 (0.41-1.27)	.24
Women	2367	2548	2029	2480	NA
All-cause mortality					
Deaths from any cause	162	134	103	130	NA
Event rate (per 1000 person-years)	11.3	7.8	6.0	6.4	NA
Unadjusted HR	1.00 [ref]	0.70 (0.49-1.00)	**0.53 (0.37-0.76)**	**0.55 (0.40-0.77)**	.001
Multivariate-adjusted HR, model 1	1.00 [ref]	0.73 (0.53-1.03)	**0.55 (0.38-0.79)**	**0.54 (0.38-0.77)**	.001
Multivariate-adjusted HR, model 2	1.00 [ref]	0.73 (0.53-1.03)	**0.53 (0.37-0.76)**	**0.56 (0.40-0.80)**	.002
Multivariate-adjusted HR, model 3	1.00 [ref]	0.74 (0.53-1.02)	**0.53 (0.37-0.77)**	**0.58 (0.41-0.81)**	.002
Cardiovascular mortality					
Deaths from any cause	30	27	23	20	NA
Event rate (per 1000 person-years)	2.0	1.5	1.0	1.1	NA
Unadjusted HR	1.00 [ref]	0.79 (0.38-1.61)	0.52 (0.25-1.05)	0.54 (0.28-1.01)	.03
Multivariate-adjusted HR, model 1	1.00 [ref]	0.84 (0.41-1.67)	0.52 (0.25-1.08)	**0.49 (0.25-0.97)**	.02
Multivariate-adjusted HR, model 2	1.00 [ref]	0.86 (0.43-1.72)	0.48 (0.22-1.04)	**0.48 (0.25-0.93)**	.01
Multivariate-adjusted HR, model 3	1.00 [ref]	0.85 (0.43-1.68)	0.48 (0.23-1.02)	0.53 (0.28-1.01)	.03
Noncardiovascular mortality					
Deaths from any cause	132	107	80	108	NA
Event rate (per 1000 person-years)	9.3	6.2	4.9	5.2	NA
Unadjusted HR	1.00 [ref]	0.68 (0.45-1.02)	**0.53 (0.35-0.81)**	**0.55 (0.37-0.82)**	.005
Multivariate-adjusted HR, model 1	1.00 [ref]	0.72 (0.49-1.04)	**0.56 (0.36-0.85)**	**0.55 (0.36-0.83)**	.005
Multivariate-adjusted HR, model 2	1.00 [ref]	0.71 (0.49-1.03)	**0.53 (0.35-0.81)**	**0.57 (0.38-0.85)**	.008
Multivariate-adjusted HR, model 3	1.00 [ref]	0.71 (0.49-1.03)	**0.54 (0.36-0.82)**	**0.58 (0.39-0.86)**	.008
Cancer mortality					
Deaths from any cause	38	38	27	40	NA
Event rate (per 1000 person-years)	2.5	2.0	1.7	1.8	NA

Continued on next page

TABLE 5. Continued

Variable	Caffeine (mg/d)				*P* value for trend[c]
	<10	10-99	100-199	≥200	
Women, continued					
Unadjusted HR	1.00 [ref]	0.80 (0.45-1.43)	0.70 (0.38-1.30)	0.72 (0.42-1.23)	.23
Multivariate-adjusted HR, model 1	1.00 [ref]	0.83 (0.45-1.50)	0.67 (0.34-1.30)	0.66 (0.37-1.17)	.14
Multivariate-adjusted HR, model 2	1.00 [ref]	0.80 (0.44-1.45)	0.59 (0.31-1.13)	0.66 (0.37-1.18)	.13
Multivariate-adjusted HR, model 3	1.00 [ref]	0.82 (0.45-1.50)	0.62 (0.32-1.20)	0.69 (0.38-1.24)	.17

[a]HR = hazard ratio; NA = not applicable; ref = reference.

[b]Data are presented as number or hazard ratio (95% CI). Boldface type indicates a significant difference ($P<.05$).

[c]*P* values for linear trend were calculated by assigning scores for categories of caffeine intake, starting from 0 for a caffeine intake of 10 mg/d to 3 for the highest intake, used as a continuous variable.

[d]Multivariate model 1 included adjustments for potential confounders as follows: age, sex, race and ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), education (less than high school, high school graduation or general education development certificate, and more than high school), current smoking status (current smoker, former smoker, and never smoked), and body mass index (<18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, and ≥35.0 kg/m^2).

[e]Multivariate model 2 included adjustments for the potential confounders of model 1 plus dyslipidemia, hypertension, diabetes, coronary heart disease, heart failure, stroke, and cancer.

[f]Multivariate model 3 included adjustments for the potential confounders of models 1 and 2 plus total daily intake of energy, carbohydrates, fat, and protein.

0.51-0.78; $P<.001$), and ≥200 mg/day (HR, 0.69; 95% CI, 0.58-0.83; $P<.001$). In addition, a similar association was observed after multivariate adjustments for the potential confounders of model 3 and health conditions (10-99 mg/d: HR, 0.90; 95% CI, 0.71-1.17; 100-199 mg/d: HR, 0.60; 95% CI, 0.48-0.74; and ≥200 mg/d: HR, 0.75; 95% CI, 0.60-0.94) and after multivariate adjustment for the potential confounders of model 3 and physical activity (10-99 mg/d: HR, 0.85; 95% CI, 0.67-1.08; 100-199 mg/d: HR, 0.68; 95% CI, 0.52-0.87; and ≥200 mg/d: HR, 0.72; 95% CI, 0.59-0.89). The HRs for all-cause mortality in the participants with complications are presented in Table 2. Compared with participants with a caffeine intake of less than 10 mg/d, the lowest HRs for all-cause mortality in multivariate model 3 were found in those with a caffeine intake of 100 to 199 mg/d (HR, 0.64; 95% CI, 0.47-0.88 for those with obesity; HR, 0.75; 95% CI, 0.56-0.98 for those with dyslipidemia; HR, 0.64; 95% CI, 0.52-0.79 for those with hypertension; HR, 0.79; 95% CI, 0.55-1.11 for those with diabetes; and HR, 0.59; 95% CI, 0.37-0.93 for those with cancer). Although a similar association was observed in the participants with diabetes, there were no significant differences between caffeine intake and all-cause mortality ($P=.17$). In the participants with coronary heart disease and/or heart failure, the HR for all-cause mortality was lowest in those with a caffeine intake of 10 to 99 mg/d (HR, 0.63; 95% CI, 0.42-0.95). The sensitivity analysis using multiple imputation in multivariate model 3 showed similar associations between caffeine intake and all-cause mortality (10-99 mg/d: HR, 0.83; 95% CI, 0.71-0.96; 100-199 mg/d: HR, 0.63; 95% CI, 0.52-0.75; and ≥200 mg/d: HR, 0.75; 95% CI, 0.64-0.87 compared with participants with a caffeine intake of <10 mg/d).

The HRs for cause-specific mortality are presented in Table 3. There was no significant association between caffeine intake and cardiovascular mortality ($P=.22$), whereas an inverse association was observed between caffeine intake and noncardiovascular mortality ($P=.002$). The adjusted HRs for noncardiovascular mortality in multivariate model 3 were significantly lower in the participants with a caffeine intake of 10 to 99 mg/d (HR, 0.74; 95% CI, 0.57-0.95), 100 to 199 mg/d (HR, 0.60; 95% CI, 0.46-0.77), and 200 mg/d or more (HR, 0.65; 95% CI, 0.53-0.80) (all $P<.001$), compared with those with a caffeine intake of less than 10 mg/d. The HRs for cancer mortality were nonsignificantly lower in the participants with a caffeine intake of 10 to 99 mg/d (HR, 0.86; 95% CI, 0.56-1.31), 100 to 199 mg/d (HR, 0.69; 95% CI, 0.47-1.04), and 200 mg/d or more (HR, 0.70; 95% CI, 0.50-1.00) (all $P=.04$). Similar HRs for cardiovascular, noncardiovascular, and cancer mortalities were observed

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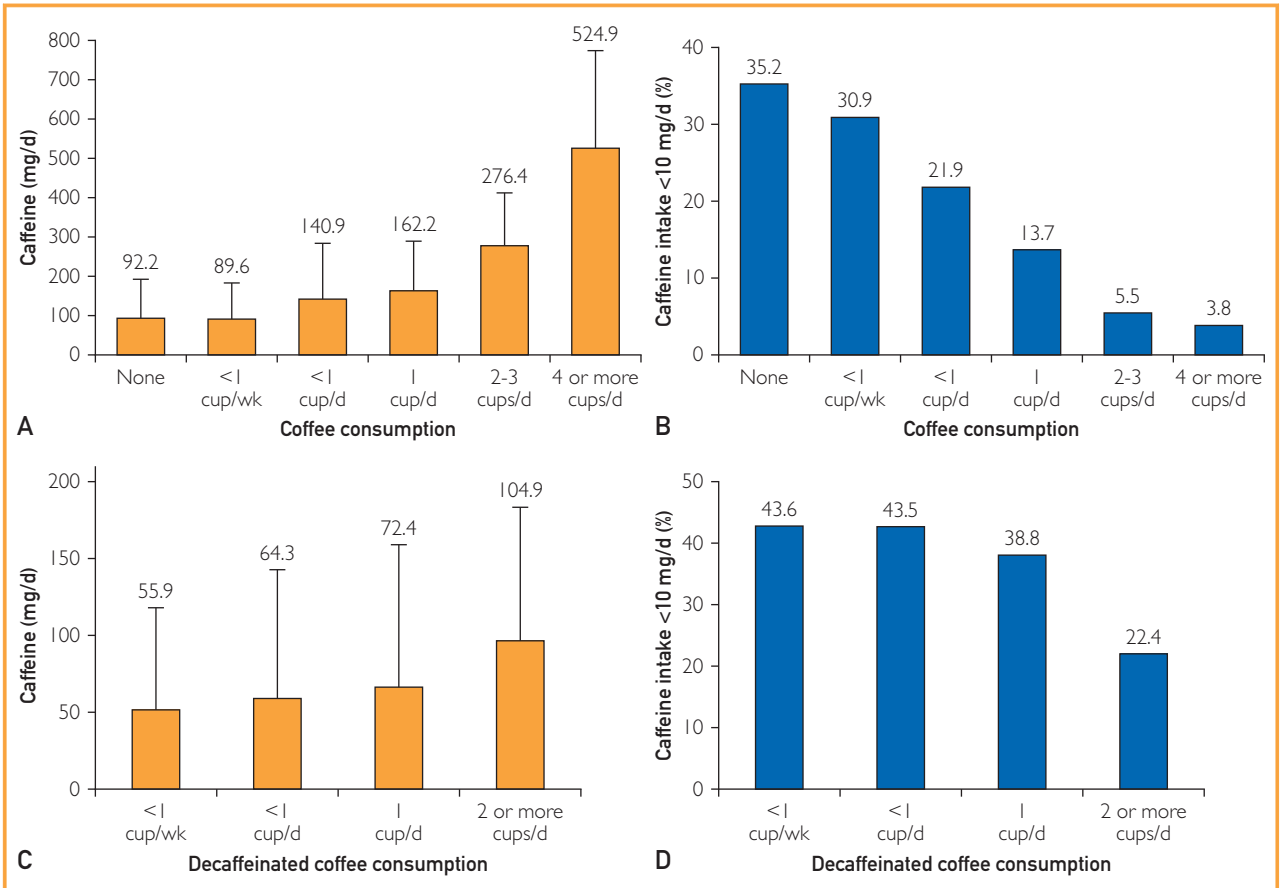

FIGURE 2. Association between coffee consumption and caffeine intake. Caffeine intake (A) and proportion of caffeine intake of less than 10 mg/d (B) according to coffee consumption. Caffeine intake (C) and proportion of caffeine intake of less than 10 mg/d (D) according to decaffeinated coffee consumption.

after multivariate adjustment with physical activity (Table 4).

Kaplan-Meier survival curves for all-cause mortality in men and women are presented in the Supplemental Figure (available online at http://www.mayoclinicproceedings.org), and the HRs for all-cause and cause-specific mortality in men and women are shown in Table 5. Compared with those with a caffeine intake of less than 10 mg/d, the adjusted HRs for all-cause mortality in multivariate model 3 were lower for men and women with a caffeine intake of 10 to 99 mg/d (men: HR, 0.90; 95% CI, 0.66-1.21; women: HR, 0.74; 95% CI, 0.53-1.02), 100 to 199 mg/d (men: HR, 0.71; 95% CI, 0.54-0.94; women: HR, 0.53; 95% CI, 0.37-0.77), and 200 mg/d or more (men: HR, 0.79; 95% CI, 0.59-1.05; women: HR, 0.58; 95% CI, 0.41-0.81). Although not all HRs were statistically significant, they were the lowest and significantly lower in both men (HR, 0.71; 95% CI, 0.54-0.94; P =.01) and women (HR, 0.53; 95% CI, 0.37-0.76; P=.001) with a caffeine intake of 100 to 199 mg/d compared with those with a caffeine intake of less than 10 mg/d. The HRs for all-cause, cardiovascular, and noncardiovascular mortality in multivariate model 3 were the lowest in those with a caffeine intake of 100 to 199 mg/d and lower in women than in men (all-cause mortality: HR, 0.71; 95% CI, 0.54-0.94 for men and HR, 0.53; 95% CI, 0.37-0.77 for women; cardiovascular mortality: HR, 1.03; 95% CI, 0.49-2.14 for men and HR, 0.48; 95% CI, 0.23-1.02 for women; noncardiovascular mortality: HR, 0.64; 95% CI, 0.48-0.85 for men and HR, 0.54; 95% CI, 0.36-0.82 for women). In the model that

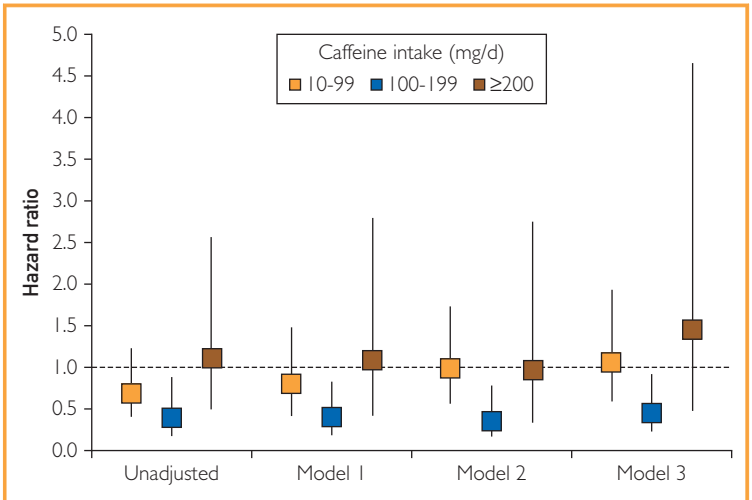

FIGURE 3. Hazard ratios for all-cause mortality according to daily caffeine intake in participants who consumed less than 1 cup of coffee per week. The reference line at 1.0 corresponds to the reference group with a caffeine intake of less than 10 mg/d.

included the interaction term between sex and caffeine intake (<10 or ≥10 mg/d), we found that the association between caffeine intake and all-cause mortality was not significantly interacted by sex (P=.11 for interaction term).

The associations between coffee consumption and caffeine intake are presented in Figure 2. Although daily caffeine intake increased with coffee consumption, about 90 mg/d of caffeine intake was found in the participants who consumed no coffee or less than 1 cup of coffee per day. The proportion of participants with a caffeine intake of less than 10 mg/d was only 30% to 35% in those who consumed no coffee or less than 1 cup of coffee per day. In addition, although daily caffeine intake increased with decaffeinated coffee consumption, participants who consumed 2 or more cups of decaffeinated coffee per day had a caffeine intake of 100 mg/d or more. Only about 40% of participants who consumed 1 or less cups of decaffeinated coffee per day had a caffeine intake of less than 10 mg/d. To exclude the potential effects of coffee components other than caffeine, the association between caffeine intake and all-cause mortality was assessed in the participants who consumed less than 1 cup of coffee per week (Figure 3). Similar associations between caffeine intake and mortality were observed in those participants. Compared with participants with a caffeine intake of <10 mg/day, the adjusted HRs for all-cause mortality in multivariate model 3 was the lowest and significantly lower in those with a caffeine intake of 100 to 199 mg/day (10-99 mg/d: HR, 1.06; 95% CI, 0.58-1.94; P=.84; 100-199 mg/d: HR, 0.46; 95% CI, 0.22-0.93; P=.03: and ≥200 mg/d: HR, 1.45; 95% CI, 0.45-4.65; P=.51).

DISCUSSION

Our analyses of nationally representative data collected from the NHANES indicated that caffeine intake was associated with a decreased risk of all-cause mortality, particularly noncardiovascular mortality. Meanwhile, there was no association between caffeine intake and cardiovascular mortality. These results indicated that competing risk might not be an explanation for decreased noncardiovascular mortality. The HR for all-cause mortality was lowest in the participants with moderate caffeine intake of 100 to 199 mg/d, and the HRs for all-cause and cause-specific mortality were lower for women than men. Furthermore, a similar association between caffeine intake and all-cause mortality was observed in the participants who consumed less than 1 cup of coffee per week.

Many studies have suggested that coffee consumption is inversely associated with all-cause and cause-specific mortality.[1-4] Coffee is a complex beverage that contains more than 1000 compounds.[21] Several studies have reported the beneficial effects of several coffee components, including caffeic acid,[22] chlorogenic acid,[23] and diterpenoids.[24] However, although decaffeinated coffee may also be inversely associated with a small reduction in all-cause mortality,[2,3,25] even decaffeinated coffee still contains caffeine in varying amounts (typical range of 5-15 mg per 8 oz).[21,26] Actually, the results of the present study revealed that the participants who drank no coffee or decaffeinated coffee consumed at least some caffeine, and caffeine intake increased with decaffeinated coffee consumption. Therefore, the results of decaffeinated coffee should not be interpreted as meaning that caffeine intake has no beneficial effects on mortality. In the present study, moderate

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caffeine intake was associated with a decreased risk of all-cause and noncardiovascular mortality, and an inverse association was observed in those who consumed no coffee. The mechanism of this association is currently unclear and may reflect mere chance or residual confounding. Possible explanations are that caffeine reduces the risk of depression,[27] stimulates the metabolic rate and has beneficial effects on weight control,[28] is a methylxanthine bronchodilator,[29] enhances performance in sustained high-intensity exercise,[30] and is associated with protective effects against some infectious[31] and malignant[32] diseases. Conversely, the present analyses found no beneficial effects of caffeine intake on cardiovascular mortality, although several studies and a recent meta-analysis found an inverse association between coffee consumption and cardiovascular mortality.[1] Caffeine intake can stimulate sympathetic activity and increase catecholamine levels,[7] leading to significant cardiovascular stress.[8] However, a previous study reported that habitual coffee consumption may not lead to cardiovascular stress, in contrast to nonhabitual coffee consumption.[7] Hence, further studies are needed to clarify how and in what form we should consume moderate amounts of caffeine.

The present study found that the HRs for all-cause and cause-specific mortality were lower for women than men. Similar findings were reported in recent studies about the inverse association between coffee consumption and all-cause and cause-specific mortality.[1,25] Possible reasons may include differences in mortality, causes of death, and levels of sex hormones, such as testosterone and estrogen, which may protect against caffeine-induced cardiac stress by attenuating vascular responses to intra-arterial norepinephrine.[33] Although all-cause mortality in the present study was not significantly associated with the interaction term for sex and caffeine intake (P=.11), further studies are warranted to elucidate differences in the effects of caffeine intake between men and women.

This study had several limitations that should be addressed. First, this was an observational study, and thus it is not possible to conclude that the inverse relationship between moderate caffeine intake and mortality reflects cause and effect. Second, caffeine intake was self-reported and may not accurately reflect long-term patterns of caffeine intake. Notwithstanding, this is the first report of beneficial effects on all-cause and noncardiovascular mortality in response to moderate caffeine intake. The results of this study indicate that moderate caffeine intake conveys potential health benefits and may have a substantial impact on the management of various diseases.

CONCLUSION

In this study, moderate caffeine intake was associated with a decreased risk of all-cause mortality, particularly noncardiovascular mortality, regardless of the presence or absence of coffee consumption.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BMI** = body mass index; **HR** = hazard ratio; **MEC** = mobile examination center; **NCHS** = National Center for Health Statistics; **NHANES** = National Health and Nutrition Examination Survey; **USDA** = US Department of Agriculture

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Correspondence: Address to Tetsuro Tsujimoto, MD, PhD, Department of Diabetes, Endocrinology, and Metabolism, Center Hospital, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan (ttsujimoto@hosp.ncgm.go.jp).

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