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Association of Coffee Consumption With All-Cause and Cardiovascular Disease Mortality

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Abstract

Objective: To evaluate the association between coffee consumption and mortality from all causes and from cardiovascular disease.

Patients and Methods: Data from the Aerobics Center Longitudinal Study representing 43,727 participants with 699,632 person-years of follow-up were included. Baseline data were collected by an in-person interview on the basis of standardized questionnaires and a medical examination, including fasting blood chemistry analysis, anthropometry, blood pressure, electrocardiography, and a maximal graded exercise test, between February 3, 1971, and December 30, 2002. Cox regression analysis was used to quantify the association between coffee consumption and all-cause and cause-specific mortality.

Results: During the 17-year median follow-up, 2512 deaths occurred (804 [32%] due to cardiovascular disease). In multivariate analyses, coffee intake was positively associated with all-cause mortality in men. Men who drank more than 28 cups of coffee per week had higher all-cause mortality (hazard ratio [HR], 1.21; 95% CI, 1.04-1.40). However, after stratification based on age, younger (<55 years old) men and women showed a significant association between high coffee consumption (>28 cups per week) and all-cause mortality after adjusting for potential confounders and fitness level (HR, 1.56; 95% CI, 1.30-1.87 for men; and HR, 2.13; 95% CI, 1.26-3.59 for women).

Conclusion: In this large cohort, a positive association between coffee consumption and all-cause mortality was observed in men and in men and women younger than 55 years. On the basis of these findings, it seems appropriate to suggest that younger people avoid heavy coffee consumption (ie, averaging >4 cups per day). However, this finding should be assessed in future studies of other populations.

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Drinking coffee has become a normal daily routine for more than half of Americans and large numbers of people worldwide. According to the latest National Coffee Drinking Study from the National Coffee Association, approximately 64% of American adults drink coffee each day, and among coffee drinkers, the average coffee consumption in the United States is 3.1 cups per day.[1] Nevertheless, coffee has long been suspected to contribute to a variety of chronic health conditions. During the past 4 decades, the association between coffee consumption and chronic health outcomes has been investigated in relation to conditions such as obesity,[2-6] hypertension,[7,8] and coronary heart disease.[9,10] However, studies on coffee consumption in relation to all-cause and cause-specific mortality are limited, and the results are often controversial. Several studies have found a positive association between higher levels of coffee consumption and all-cause and cardiovascular disease (CVD) mortality,[11-13] whereas others have found an inverse association with all-cause mortality in men and women,[14-16] in women only,[17,18] or in men only,[19-21] with some evidence suggesting that there may be a U- or J-shaped relationship between coffee drinking and health outcomes. Still, other researchers suggest that the association may not exist at all.[22-24] The objective of the present study was to investigate the effect of coffee consumption on all-cause and CVD mortality in the Aerobics Center Longitudinal Study (ACLS) cohort, with average follow-up of 16 years and a relatively large sample of men and women.

PATIENTS AND METHODS

Study Population

The ACLS is a prospective observational study and has been described in detail previously.[24,25] Between February 3, 1971, and December 30,

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2002, 44,963 individuals aged 20 to 87 years participated and returned a medical history questionnaire assessing lifestyle habits (including coffee intake) and personal and family medical history. We examined 43,727 participants (33,900 men and 9827 women; 699,632 person-years of follow-up) in the final analysis after excluding those with a history of myocardial infarction (n=54), stroke (n=11), or cancer (n=141); those with abnormal results of resting or exercise electrocardiography (n=319); those who did not achieve 85% age-predicted maximal heart rate (n=122), those who were underweight (body mass index [BMI] [calculated as weight in kilograms divided by height in meters squared] <18.5) (n=501), and those with less than 1-year mortality follow-up (n=88). All the study participants provided written informed consent. The Cooper Clinic (Dallas, Texas) Institutional Review Board reviewed and approved the study protocol annually.

Measurement of Exposure

Regular coffee consumption, expressed as number of cups per week, was assessed by a standardized questionnaire. Consumption of regular coffee was grouped as 0, 1 to 7, 8 to 14, 15 to 21, 22 to 28, and more than 28 cups per week for primary analysis.

Measurement of Outcome

All the participants were observed for mortality from the baseline examination to the date of death or December 31, 2003. All-cause mortality and CVD mortality were identified through the National Death Index or by accessing the death certificates in the decedents' states of residence. The CVD mortality was determined using *International Classification of Diseases, Ninth Revision* codes 390 to 449.9 before 1999 and *Tenth Revision* codes 100 to 178 between 1999 and 2003.

Measurement of Covariates

All the participants underwent a baseline clinical examination at the Cooper Clinic between February 3, 1971, and December 30, 2002. The medical examination was performed after an overnight fast (>12 hours) and included fasting blood chemistry analysis, personal and family health history, anthropometry, blood pressure, electrocardiography, and a maximal graded exercise test. Responses to a standardized questionnaire were used to assess smoking status; alcohol consumption; regular tea, regular and decaffeinated coffee, and decaffeinated or herbal tea drinking (cups per week); physical activity; and parental history of CVD. Medical conditions, including hypertension, hypercholesterolemia, diabetes, cancer, myocardial infarction, and stroke, were evaluated using a standardized questionnaire.

Cardiorespiratory fitness (CRF) was quantified by the total time of the treadmill test using a modified Balke protocol.[25] Participants were encouraged to reach their maximal effort, and the test was terminated when the participant requested to stop because of exhaustion or when the physician stopped the test for medical reasons. Maximal metabolic equivalents (1 metabolic equivalent = 3.5 mL of oxygen uptake per kilogram per minute) were estimated from the final treadmill speed and grade.[26]

Statistical Analyses

Baseline characteristics of the population were estimated by baseline coffee consumption categories and sex status. Hazard ratios and 95% CIs for mortality associated with coffee consumption were estimated using Cox proportional hazards regression models, with person-years as the underlying time metric; models also were stratified by age and BMI using the same underlying time metric. The proportional hazards assumption was tested by Martingale-based residuals, and the observed results satisfied the assumption. Analyses were conducted using SAS software version 9.3 (SAS Institute, Inc). Statistical tests were 2-sided, and significance was set at α=.05. Risk estimates are presented separately for men and women. Multivariate models were adjusted for age, baseline examination year, decaffeinated coffee use, regular tea use, decaffeinated or herbal tea use, physical inactivity, BMI, smoking, alcohol consumption, diabetes, hypertension, hypercholesterolemia, parental history of CVD, and CRF. Hazard ratios for death associated with categories of coffee consumption (1-7, 8-14, 15-21, 22-28, and >28 cups per week) were compared with that for no coffee consumption. In stratified analyses, we categorized age and BMI into 2 groups (age <55 years and age ≥55 years and BMI <25 and BMI ≥25). The covariates were the same as in the main analysis.

TABLE 1. Baseline Characteristics of the Male Study Participants by Weekly Coffee Consumption[a,b]

Characteristic	Overall (N=33,900)	Coffee consumption (cups/wk)						*P* value
		0 (n=6387)	1-7 (n=6772)	8-14 (n=7045)	15-21 (n=1766)	22-28 (n=7559)	>28 (n=4371)	
Age (y), mean ± SD	43.37±9.25	41.43±9.76	43.03±9.98	43.97±9.19	43.88±8.67	44.29±8.27	44.58±8.17	<.001
Body mass index, mean ± SD	26.40±3.70	26.00±3.90	26.32±3.93	26.47±3.62	26.56±3.55	26.58±3.43	26.70±3.47	<.001
Total cholesterol (mg/dL), mean ± SD	208.48±39.40	201.90±37.97	205.16±39.97	209.37±39.23	211.89±39.17	213.10±39.51	214.53±39.36	<.001
Fasting blood glucose (mg/dL), mean ± SD	99.95±16.10	98.85±16.50	99.61±15.60	100.22±15.40	100.29±16.73	100.24±13.97	101.10±17.74	<.001
Systolic blood pressure (mm Hg), mean ± SD	121±13	121±13	122±13	122±13	121±13	121±13	121±13	<.001
Diastolic blood pressure (mm Hg), mean ± SD	81±9	81±9	81±10	81±10	81±9	81±9	81±9	.004
Cardiorespiratory fitness (maximal METs), mean ± SD	11.74±2.40	12.08±2.54	11.98±2.47	11.75±2.33	11.57±2.33	11.44±2.25	11.15±2.17	<.001
Maximal treadmill time (min), mean ± SD	18.10±4.89	18.78±5.08	18.61±4.99	18.16±4.79	17.77±4.78	17.51±4.69	16.91±4.58	<.001
Drink decaffeinated coffee (%)	9.26	5.71	17.90	10.82	6.77	5.01	3.86	<.001
Drink regular tea (%)	57.01	50.27	60.56	57.70	59.83	56.15	55.93	<.001
Drink decaffeinated/herbal tea (%)	4.53	6.89	7.15	4.03	2.82	2.28	1.37	<.001
Alcohol heavy drinker (%)[c]	7.62	4.43	6.67	7.66	9.30	10.47	9.68	<.001
Current smoker (%)	18.18	10.71	13.50	17.73	23.75	25.53	31.85	<.001
Physical inactivity (%)[d]	29.47	28.60	24.31	26.91	31.26	35.24	38.65	<.0001
Diabetes (%)[e]	5.26	4.78	5.38	5.70	5.18	4.86	5.46	.20
Hypercholesterolemia (%)[f]	26.61	22.25	26.11	27.99	28.08	28.34	28.31	<.001
Hypertension (%)[g]	30.36	29.12	31.08	31.26	30.21	29.10	30.53	<.001
Parental history of CVD (%)	26.52	23.56	25.10	26.27	27.75	28.91	30.93	.045

[a]CVD = cardiovascular disease; MET = metabolic equivalent.
[b]SI conversion factors: To convert total cholesterol values to mmol/L, multiply by 0.0259; to convert fasting blood glucose values to mmol/L, multiply by 0.0555.
[c]Alcohol heavy drinker is defined as more than 14 alcoholic drinks per week for men and more than 7 per week for women.
[d]Physical inactivity is defined as no leisure time physical activity during the past 3 months.
[e]Diabetes is defined as a fasting glucose level of at least 126 mg/dL, physician-diagnosed diabetes, or insulin use.
[f]Hypercholesterolemia is defined as a total cholesterol level of at least 240 mg/dL or physician-diagnosed hypercholesterolemia.
[g]Hypertension is defined as resting blood pressure of at least 140/90 mm Hg or physician-diagnosed hypertension.

RESULTS

During the 17-year median follow-up, 2512 deaths occurred (2198 men [87.5%] and 314 women [12.5%]), and 804 (32%) were caused by CVD. Tables 1 and 2 show the association between coffee consumption and participants' characteristics at baseline. Men and women who consumed higher amounts of coffee were more likely to smoke and had lower levels of CRF.

Coffee Consumption and All-Cause Mortality

The hazard ratios for all-cause mortality in coffee consumption groups are shown in Table 3. In the age-adjusted analyses, compared with men who did not drink coffee, men who drank coffee at a rate of 8 to 14, 15 to 21, and more than 28 cups per week had a higher risk of all-cause mortality. In the multivariable-adjusted model, men who consumed more than 28 cups of coffee per week had the highest risk of all-cause mortality. This association persisted in the final model, which further adjusted for CRF level. However, coffee consumption was not associated with all-cause mortality risk in women. Kaplan-Meier survival curves indicate that women (Figure 1, A) and men (Figure 1, B) with higher coffee consumption had lower mortality-free time compared with those who did not drink coffee.

Coffee Consumption and CVD-Related Mortality

The hazard ratios for CVD-related mortality in coffee consumption groups are shown in Table 3. In the age-adjusted analyses, compared with men who did not drink coffee, men who

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TABLE 2. Baseline Characteristics of the Female Study Participants by Weekly Coffee Consumption[a,b]

Characteristic	Overall (N=9827)	Coffee consumption (cups/wk)						*P* value
		0 (n=2025)	1-7 (n=2823)	8-14 (n=1440)	15-21 (n=249)	22-28 (n=2602)	>28 (n=688)	
Age (y), mean ± SD	42.97±10.10	40.35±10.32	42.65±10.74	44.07±9.70	44.40±9.00	44.91±9.45	43.77±8.67	<.001
Body mass index, mean ± SD	23.15±3.86	23.02±4.09	23.21±3.94	23.29±3.97	22.98±3.44	23.05±3.27	23.10±3.51	.08
Total cholesterol (mg/dL), mean ± SD	198.34±40.56	193.77±36.10	197.39±46.83	199.50±38.48	202.14±37.32	202.77±38.26	201.11±38.68	<.001
Fasting glucose (mg/dL), mean ± SD	94.60±96.43	92.73±15.06	97.00±178.00	93.79±12.07	93.75±12.41	95.80±20.73	93.84±10.59	.75
Systolic blood pressure (mm Hg), mean ± SD	112±14	112±14	112±14	113±14	112±14	112±14	110±14	.02
Diastolic blood pressure (mm Hg), mean ± SD	75±9	75±9	75±9	76±9	76±9	75±9	75±9	.03
Cardiorespiratory fitness (maximal METs), mean ± SD	9.61±2.14	9.90±2.16	9.81±2.16	9.57±2.16	9.44±2.09	9.30±2.05	9.18±1.93	<.001
Maximal treadmill time (min), mean ± SD	13.60±4.60	13.76±4.63	14.03±4.61	13.51±4.63	13.21±4.51	12.93±4.44	12.67±4.2	<.001
Drink decaffeinated coffee (%)	12.77	10.42	21.68	10.95	7.36	6.09	2.60	<.001
Drink regular tea (%)	53.15	48.40	57.21	54.07	52.50	49.58	49.67	<.001
Drink decaffeinated/herbal tea (%)	12.83	17.88	16.08	11.18	7.08	7.56	3.47	<.001
Alcohol heavy drinker (%)[c]	9.56	6.07	9.07	11.91	11.60	10.08	7.59	<.001
Current smoker (%)	10.66	7.31	7.93	11.03	13.06	19.12	23.86	<.001
Physical inactivity (%)[d]	26.09	26.67	23.84	25.13	27.78	29.83	33.62	<.001
Diabetes (%)[e]	3.25	3.46	3.33	3.31	2.71	3.78	2.60	.79
Hypercholesterolemia (%)[f]	19.18	16.54	19.06	20.56	20.83	18.28	19.52	.01
Hypertension (%)[g]	15.71	15.46	14.84	16.87	16.32	16.18	13.23	<.001
Parental history of CVD (%)	26.20	20.79	26.11	27.98	29.72	28.15	27.55	.22

[a]CVD = cardiovascular disease; MET = metabolic equivalent.
[b]SI conversion factors: To convert total cholesterol values to mmol/L, multiply by 0.0259; to convert fasting blood glucose values to mmol/L, multiply by 0.0555.
[c]Alcohol heavy drinker is defined as more than 14 alcoholic drinks per week for men and more than 7 per week for women.
[d]Physical inactivity is defined as no leisure time physical activity during the past 3 months.
[e]Diabetes is defined as a fasting glucose level of at least 126 mg/dL, physician-diagnosed diabetes, or insulin use.
[f]Hypercholesterolemia is defined as a total cholesterol level of at least 240 mg/dL or physician-diagnosed hypercholesterolemia.
[g]Hypertension is defined as resting blood pressure of at least 140/90 mm Hg or physician-diagnosed hypertension.

drank coffee at a rate of more than 28 cups per week had a 36% higher risk of CVD mortality. However, this association disappeared in the final model, which adjusted for potential confounders and CRF level. For women, coffee consumption was not associated with CVD mortality risk in any model.

Coffee Consumption and All-Cause Mortality by Age Group

The associations between coffee consumption and all-cause mortality for younger and older age groups are depicted in Figure 2. Figure 2, A shows that younger men who consumed coffee at a rate of 8 to 14, 15 to 21, and more than 28 cups per week had higher risks of all-cause mortality than did those who did not drink coffee, after adjusting for the potential confounders and CRF level. The hazard ratio of all-cause mortality for younger men (<55 years old) who drank more than 28 cups per week is 1.56 (95% CI, 1.30-1.87). The final model indicated that younger women who consumed more than 28 cups of coffee per week also had a higher risk of all-cause mortality than did those who did not drink coffee (hazard ratio, 2.13; 95% CI, 1.26-3.59). However, coffee consumption was not associated with all-cause mortality in older men and women (Figure 2, B).

Coffee Consumption and All-Cause Mortality by BMI Group

The only marginally significant association of coffee consumption and all-cause mortality

TABLE 3. Association (Hazard Ratio [95% CI]) of Coffee Consumption With All-Cause and Cardiovascular Disease (CVD) Mortality

Coffee consumption (cups/wk)	Men			Women		
	Model 1[a]	Model 2[b]	Model 3[c]	Model 1[a]	Model 2[b]	Model 3[c]
All-cause mortality						
0	1	1	1	1	1	1
1-7	1.11 (0.96-1.28)	1.09 (0.94-1.27)	1.09 (0.94-1.27)	0.73 (0.51-1.06)	0.73 (0.50-1.05)	0.73 (0.50-1.06)
8-14	1.23 (1.07-1.41)	1.14 (0.99-1.31)	1.14 (0.99-1.31)	1.10 (0.80-1.52)	1.04 (0.75-1.44)	1.05 (0.76-1.46)
15-21	1.16 (1.01-1.33)	1.05 (0.91-1.20)	1.04 (0.91-1.19)	0.88 (0.61-1.26)	0.86 (0.59-1.24)	0.85 (0.58-1.22)
22-28	1.16 (0.97-1.38)	1.04 (0.87-1.24)	1.03 (0.86-1.23)	1.11 (0.68-1.81)	1.03 (0.63-1.69)	1.04 (0.63-1.71)
>28	1.41 (1.22-1.64)	1.22 (1.05-1.42)	1.21 (1.04-1.40)	1.35 (0.88-2.08)	1.22 (0.78-1.89)	1.21 (0.78-1.88)
P for linear trend	<.001	.06	.09	.13	.36	.37
Cardiovascular disease mortality						
0	1	1	1	1	1	1
1-7	1.05 (0.81-1.35)	1.02 (0.79-1.32)	1.02 (0.79-1.32)	0.83 (0.39-1.79)	0.87 (0.40-1.89)	0.87 (0.40-1.90)
8-14	1.16 (0.92-1.47)	1.03 (0.81-1.31)	1.03 (0.81-1.30)	1.41 (0.73-2.72)	1.27 (0.64-2.49)	1.29 (0.66-2.54)
15-21	1.16 (0.92-1.47)	1.02 (0.80-1.29)	1.01 (0.80-1.28)	0.96 (0.45-2.09)	0.94 (0.43-2.05)	0.92 (0.42-2.01)
22-28	1.14 (0.85-1.54)	1.02 (0.75-1.38)	1.01 (0.75-1.37)	1.06 (0.35-3.24)	0.92 (0.30-2.84)	0.97 (0.31-2.99)
>28	1.36 (1.06-1.76)	1.16 (0.90-1.50)	1.15 (0.89-1.49)	0.89 (0.29-2.71)	0.72 (0.23-2.24)	0.73 (0.23-2.27)
P for linear trend	.02	.29	.93	.02	.23	.19

[a]Model 1 was adjusted for age and baseline examination year.

[b]Model 2 was adjusted for age, baseline examination year, decaffeinated coffee use, regular tea use, decaffeinated or herbal tea use, physical inactivity, body mass index, smoking, alcohol consumption, diabetes, hypertension, hypercholesterolemia, and family history of CVD.

[c]Model 3 includes all the covariates in model 2 and additional covariates for fitness.

was observed in men with a BMI of at least 25 who consumed more than 28 cups of coffee per week, indicating that overweight/obese men who consumed more than 28 cups of coffee per week had slightly higher all-cause mortality risk than those who did not drink coffee. Because of sample size limitations, we could not further investigate this association on the basis of additional age stratification.

DISCUSSION

Key Findings

We found that coffee intake was positively associated with higher all-cause mortality in men, but only a suggestion of an effect was found in women. In men, those who drank more than 28 cups of coffee weekly had a 21% higher risk of dying compared with their non–coffee-consuming peers. Neither men nor women had significant associations between CVD mortality and coffee consumption. The results of the stratified analysis showed that younger men and women who consumed more than 28 cups of coffee per week had a higher risk of all-cause mortality than those who did not drink coffee, after adjusting for the potential confounders and CRF level. For people, particularly men, who were overweight or obese, coffee consumption trended positively, although not significantly, on all-cause mortality. We did not conduct stratified analyses on the basis of CVD mortality because of the null findings between coffee consumption and CVD death.

Comparison With Other Studies

The present findings for all-cause mortality are consistent with those of earlier studies,[11,13,20,21] but the results of recent studies have been highly variable.[15-17,23,27] Most inverse associations between coffee consumption and mortality were observed from studies on the basis of middle-aged or older populations. Freedman et al[16] found an inverse association between coffee consumption and all-cause mortality after adjusting for potential confounders. Lopez-Garcia et al[23] also found an inverse association in men. However, Kleemola et al[18] found this inverse association only in women. One possible explanation for this inverse association between coffee consumption and all-cause mortality might be survival selection because the results of most of the previous studies are based on older or middle-aged populations. The present study, however, had a very wide age range, from 20 to 87 years, so the survival selection might be smaller. Our stratified analyses also

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support this explanation. Figure 2 shows that younger men and women had an increased risk of mortality for heavy coffee drinking (>28 cups per week) compared with non–coffee drinkers. In addition, the non–coffee-drinking group may have had a higher mortality risk not related to the consumption of coffee; however, those unknown factors may exert an inverse effect on the association between coffee consumption and mortality. No statistically significant association was found between coffee consumption and CVD mortality in this study. Some cohort studies also have examined the effect of coffee consumption on CVD mortality, and the results have been variable, somewhat similar to the situation with all-cause mortality in our study.

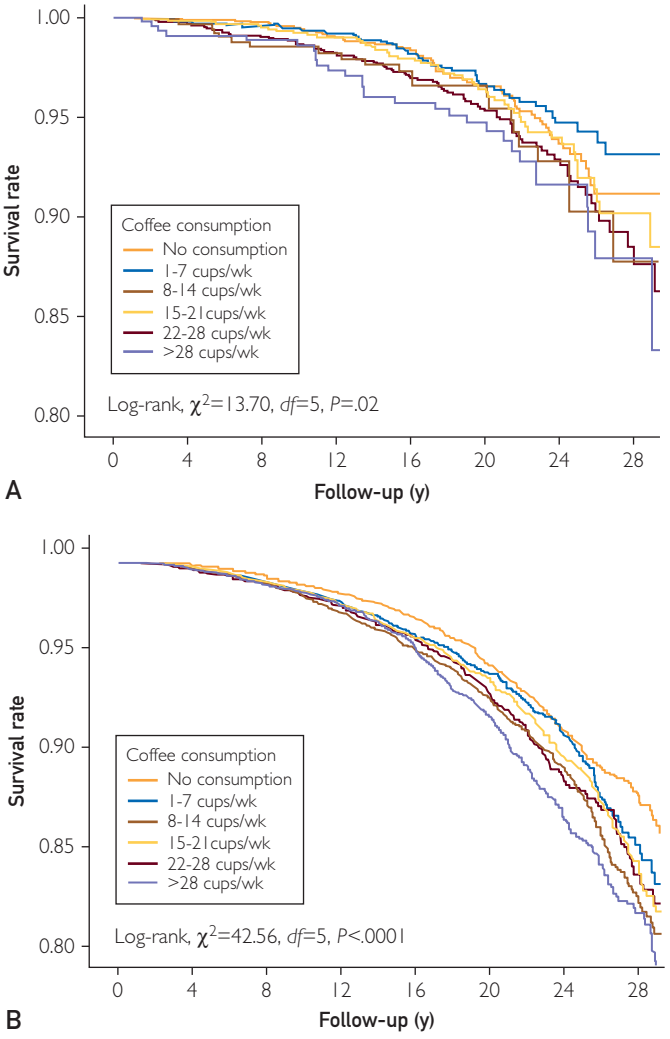

FIGURE 1. Kaplan-Meier plots of all-cause mortality due to coffee consumption, Aerobics Center Longitudinal Study, 1971-2003, in (A) women and (B) men.

Possible Mechanism

Coffee is a complex mixture of chemicals consisting of thousands of components.[28] Recent research has found that coffee is one of the major sources of antioxidants in the diet[29,30] and has potential beneficial effects on inflammation.[31,32] However, it is also well known that coffee has potential adverse effects because of caffeine's potential to stimulate the release of epinephrine,[33] inhibit insulin activity,[34] and increase blood pressure and homocysteine levels.[35] Thus, all of these mechanisms could counterbalance one another. Research also suggests that heavy coffee drinkers may experience additional risk through potential genetic mechanisms[36] or because of confounding through the deleterious effects of other risk factors with which coffee drinking is associated. Genetic factors may partly explain why moderate coffee consumption is not as likely to be associated with increased mortality, whereas heavy coffee consumption could lead to increased mortality, as was especially noted in the men in this study. Therefore, we hypothesize that the positive association between coffee and mortality may be due to the interaction of age and coffee consumption, combined with a component of genetic coffee addiction.

Strengths

There are several strengths of this study. First, it examined a large cohort, including 43,727 participants of both sexes and with a wide age range from 20 to almost 90 years. Although most of the study population was white, highly educated, and from middle to upper social economic status, the homogeneity of the study population enhanced the internal validity. Second, we were able to control for potential confounders, including physical activity and CRF. Third, subclinical disease is unlikely to be a major problem in this study because we excluded people who had baseline CVD, cancer, underweight, and abnormal electrocardiographic findings, and we controlled for major chronic diseases, such as hypertension, diabetes, and hypercholesterolemia in the analysis. Fourth, the possibility that reverse causality may bias the results is small because the current study is prospective cohort.

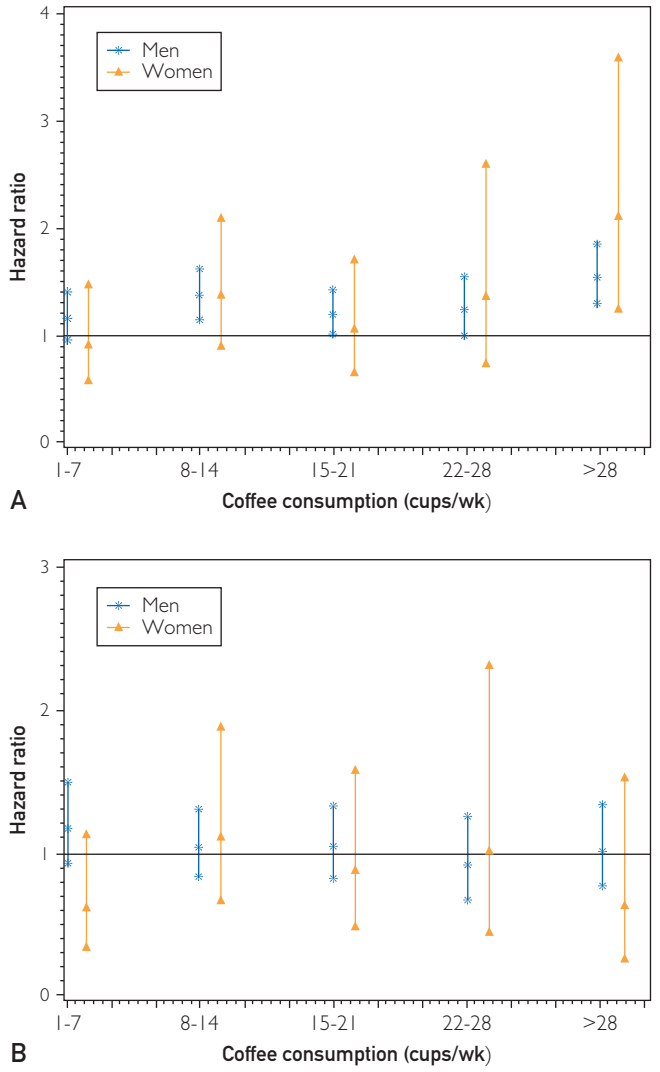

FIGURE 2. Multivariate-adjusted hazard ratios and 95% CIs between coffee consumption and all-cause mortality for men and women (A) younger than 55 years and (B) 55 years and older.

Limitations

On the other hand, this study does have certain limitations. First, this study did not have repeated measures of coffee consumption over time, which prevents analysis of long-term coffee consumption patterns and changes in coffee consumption over time. However, several studies have examined long-term habitual coffee intake and have found that coffee drinking, besides being easy to measure, tends to be stable in adulthood[23,37] and that a single point measurement of coffee consumption is a valid indicator for long-term coffee consumption.[38] Still, future studies with repeated measures of coffee consumption are warranted to elucidate the effect of change in coffee consumption on longevity. Second, we did not have data on coffee preparation methods, and the constituents of coffee may differ, which might also impact its potential association with CVD risk factors on the basis of the different preparation methods. Third, data on marital status and total energy consumption were not included in the present study. Although educational level is not available for the analysis,[39] we reported previously that the ACLS population is highly educated and homogeneous, which in fact increases the study's internal validity. Fourth, residual confounding may still exist even though we adjusted for all the potential confounders available in the present study. Smoking is likely to be one of the most important factors to cause residual confounding in this investigation. We therefore stratified the analysis by smoking status and the results are shown in Supplemental Figures 1 and 2, available online at http://www.mayoclinicproceedings.org. We did not observe the significant association between coffee consumption and all-cause mortality both in current smokers and non-current smokers. Finally, a cohort effect might still exist even though we included the baseline examination year as a way to control for it. A recent ACLS report by Willis et al[40] examining the secular change across different decades when participants entered the ACLS study, from the 1970s, 1980s, 1990s, and 2000s, revealed that there was little change in participants' characteristics, such as age, BMI, blood profile, and chronic disease over time. However, to remove or control for the possible cohort effect, we included the baseline examination year as a covariate,which is a general approach that we have applied in most of our ACLS analyses.

CONCLUSION

In this large US cohort study, a positive association between heavy coffee consumption (>28 cups per week) and all-cause mortality was observed in the total population of men and in men and women younger than 55 years. However, for people 55 years and older, this association was not statistically significant for either sex. Hence, it may be appropriate to recommend that younger people, in particular, avoid heavy coffee consumption (>28 cups per week or >4 cups in a typical day). Further

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studies are needed to assess details regarding the effects of long-term coffee consumption and changes in coffee consumption over time on all-cause and CVD mortality.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

Abbreviations and Acronyms: **ACLS** = Aerobics Center Longitudinal Study; **BMI** = body mass index; **CRF** = cardiorespiratory fitness; **CVD** = cardiovascular disease

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