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ORIGINAL ARTICLE

Epidemiology

Coffee Consumption and All-Cause and Cardiovascular Mortality

— Three-Prefecture Cohort in Japan —

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Background: Coffee, which contains various bioactive compounds, is one of the most popular beverages. Further accumulation of evidence is needed, however, to confirm whether coffee consumption would be effective in preventing cardiovascular disease in the general Japanese population.

Methods and Results: We evaluated the association between coffee consumption frequency (never, sometimes, 1–2 cups/day, 3–4 cups/day and ≥5 cups/day) and mortality from all causes, heart disease, and cerebrovascular disease, in 39,685 men and 43,124 women aged 40–79 years at baseline, in a 3-prefecture cohort study. The coffee consumption frequency was assessed on questionnaire. Cox proportional hazards regression modeling was used to assess the association between coffee consumption frequency and all-cause and cardiovascular disease mortality with adjustment for potential confounders. During 411,341 and 472,433 person-years in men and women, respectively, a total of 7,955 men and 5,725 women died. Coffee consumption frequency was inversely associated with all-cause mortality in both genders (P for trend<0.001). In addition, the risks of mortality from cerebrovascular disease in men (P for trend<0.001), and heart disease in women (P for trend=0.031) were inversely associated with coffee consumption.

Conclusions: In this Japanese population, coffee drinking has a preventive effect on all-cause and on cardiovascular mortality in men and/or women.

Key Words: Cardiovascular disease; Coffee consumption; Cohort; Japanese; Mortality

Coffee is one of most popular beverages; and almost 40% of adults drink at least 1 cup of coffee daily, in Japan.[1,2] Coffee drinking provides exposure to many bioactive compounds,[3] and higher consumption has been linked to an anti-inflammatory effect by caffeine and chlorogenic acids.[4,5] Therefore, regular coffee drinking, over the life course, may provide a beneficial effect in healthy people.

Recent meta-analysis on the association between coffee drinking and all-cause mortality reported that moderate coffee intake is associated with reduced risk of death from all causes.[6,7] In addition, coffee intake affected the risk of all or various sites of cancers in previous studies, including meta-analyses[7–12] and ours.[13] Subsequent cohort studies have also shown that coffee intake is associated with lower risk for all-cause death.[1,14–17] In Japan, 3 large population-based cohort studies reported an inverse association between coffee consumption and all-cause mortality[1,2,18] or cardiovascular disease mortality.[1,18,19] Cardiovascular

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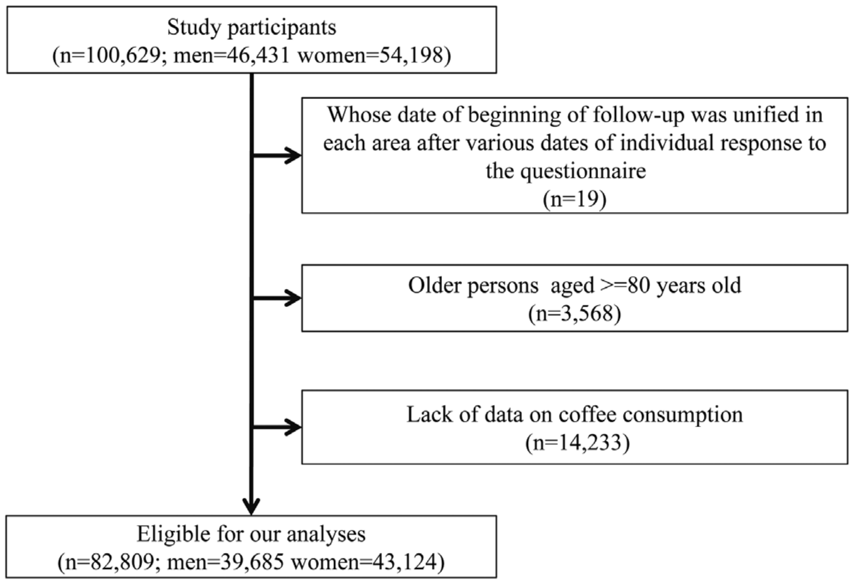

Figure. Flowchart of participant selection.

disease mortality is the second or third highest cause of death in Japan.[20] Importantly, studies on the association between coffee consumption and all-cause and cardiovascular mortality have been reported from cohorts in Western countries even in recent years.[15–17,21] Therefore, assessing this association is an important topic in cardiovascular preventive epidemiology. Further accumulation of evidence is therefore needed to confirm whether coffee consumption would be effective in preventing cardiovascular disease in the general Japanese population.

Using the database of the Three-Prefecture Cohort,[22,23] which was a large-scale prospective cohort study of almost 100,000 inhabitants living in both urban and rural areas of Japan, we investigated the association between coffee consumption and all-cause and cardiovascular disease mortality. We evaluated the hypothesis that high coffee consumption would be associated with reduced risk of all-cause and cardiovascular disease mortality, among this population.

Methods

Study Design, Settings, and Patients

Details of this target population and baseline survey method have been described previously.[22,23] The Three-Prefecture Cohort Study was launched in 1983, 1984, and 1985 for Osaka, Miyagi, and Aichi Prefecture areas, respectively. The main aim of that cohort study was to assess the long-term effects of air pollution on mortality from lung cancer and respiratory diseases and also to investigate the association between lifestyle and various disease. In brief, the study areas were either urban or rural, in these prefectures. The study subjects were all residents aged ≥40 years, and the total number of the population was 139,008. Overall, 117,029 self-administered questionnaires in sealed envelopes were distributed by hand to targeted individuals in cooperation with the municipal government, in each area, during the starting period, with a total number of 104,567 responders (response rate, 89.3%), of whom, 100,629 (final participation rate, 86.0%) were included as subjects in this cohort. Subjects with duplicated questionnaires or who did not include their name/gender/date of birth, were excluded because investigators could not follow up the outcome data. We conducted this study in compliance with the declaration of Helsinki and ethics guidelines for epidemiological research. The institutional review board of the National Cancer Center and the Ethics Committee of Osaka University School of Medicine approved the study. The agreement or permission for the municipality residents' baseline survey was obtained from the municipal government, as collaborators. Response to the questionnaire by participants was assumed to be agreement to participate in the survey. In addition, the study committee, consisting of health center directors, local officials, and residents' association representatives, was established to protect personal information of the participants and ensure the accuracy of the study. Currently, Tohoku University, Aichi Cancer Center, and Osaka Medical Center for Cancer and Cardiovascular Diseases had information on baseline surveys, linked with information on cancer incidence and cause of death, and altered to unlinkable anonymized data. National Cancer Center integrated these datasets and managed unlinkable anonymized data. In the Three-Prefecture Cohort study, researchers analyzed only unlinkable anonymous data.

In this study, the inclusion criteria were as follows: availability of information on coffee consumption frequency, follow-up period ≥1 day, and age 40–79 years at baseline. We excluded 19 persons whose follow-up start dates (unified in each area) occurred after various dates of individual response to the questionnaire; 3,568 persons aged ≥80 years; and 14,233 persons who failed to provide answers on coffee consumption. Finally, the subjects consisted of 82,809 subjects (39,685 men and 43,124 women; **Figure**).

Follow-up

The follow-up period was defined as 15 years from the baseline survey, in each study area. The local government, using residence certificates, confirmed the date of death, vital status, and the date of moving out of the study area. The cause of death was identified from the death certificates.

Key Group Definition

In the self-reported questionnaire, in Aichi and Osaka Prefectures, coffee consumption frequency was distinguished between instant and brewed coffee. Coffee consumption was categorized as follows: never; sometimes; 1–2 cups/day; 3–4 cups/day; and ≥5 cups/day, for each coffee type. In Miyagi Prefecture, coffee consumption had 1 variable, which did not distinguish between the coffee types; and the coffee consumption categories were never; sometimes; 1–2 cups/day; 3–4 cups/day; and ≥5 cups/day. Therefore, we merged the 2 variables of coffee consumption frequency (**Supplementary Table 1**). Finally, coffee consumption was categorized as never; sometimes; 1–2 cups/day; 3–4 cups/day; and ≥5 cups/day, for each subject (**Supplementary Table 1**).

Table 1. Baseline Characteristics vs. Coffee Consumption in Men and Women

	Total	Never	Sometimes	1–2 cups/day	3–4 cups/day	≥5 cups/day	P-value
Men	39,685	(n=5,072)	(n=12,497)	(n=14,760)	(n=5,380)	(n=1,976)	
Age (years)	53 (46–61)	56 (49–66)	55 (48–64)	52 (45–60)	49 (44–57)	50 (44–57)	<0.001
Prefecture							<0.001
Miyagi	10,513 (26.5)	1,978 (39.0)	4,359 (34.9)	2,943 (19.9)	828 (15.4)	405 (20.5)	
Aichi	14,346 (36.1)	1,299 (25.6)	4,024 (32.2)	6,362 (43.1)	2,075 (38.6)	586 (29.7)	
Osaka	14,826 (37.4)	1,795 (35.4)	4,114 (32.9)	5,455 (37.0)	2,477 (46.0)	985 (49.8)	
Areas							<0.001
Rural	17,553 (44.2)	2,545 (50.2)	5,772 (46.2)	6,010 (40.7)	2,350 (43.7)	876 (44.3)	
Urban	22,132 (55.8)	2,527 (49.8)	6,725 (53.8)	8,750 (59.3)	3,030 (56.3)	1,100 (55.7)	
BMI (kg/m²)	22.5 (20.7–24.3)	22.4 (20.5–24.3)	22.6 (20.8–24.4)	22.5 (20.7–24.2)	22.4 (20.7–24.2)	22.3 (20.5–24.3)	<0.001
Current smoker	23,143 (58.3)	2,355 (46.4)	6,273 (50.2)	9,082 (61.5)	3,903 (72.5)	1,530 (77.4)	<0.001
Current drinker	19,478 (49.1)	2,560 (50.5)	6,022 (48.2)	7,539 (51.1)	2,552 (47.4)	805 (40.7)	<0.001
Rice consumption ≥3 bowls/day	28,015 (70.6)	3,584 (70.7)	9,078 (72.6)	10,297 (69.8)	3,746 (69.6)	1,310 (66.3)	<0.001
Bread consumption almost every day	11,028 (27.8)	826 (16.3)	2,248 (18.0)	5,049 (34.2)	2,117 (39.3)	788 (39.9)	<0.001
Meat consumption almost every day	6,264 (15.8)	679 (13.4)	1,752 (14.0)	2,396 (16.2)	1,006 (18.7)	431 (21.8)	<0.001
Fish consumption almost every day	9,620 (24.2)	1,608 (31.7)	3,363 (26.9)	3,124 (21.2)	1,064 (19.8)	461 (23.3)	<0.001
Egg consumption almost every day	12,696 (32.0)	1,667 (32.9)	3,947 (31.6)	4,659 (31.6)	1,746 (32.5)	677 (34.3)	0.001
Milk consumption almost every day	12,324 (31.1)	1,776 (35.0)	3,992 (31.9)	4,630 (31.4)	1,363 (25.3)	563 (28.5)	<0.001
Green and yellow vegetable consumption almost every day	15,078 (38.0)	2,223 (43.8)	4,973 (39.8)	5,336 (36.2)	1,805 (33.6)	741 (37.5)	<0.001
Non-green and non-yellow vegetable consumption almost every day	20,700 (52.2)	2,881 (56.8)	6,823 (54.6)	7,471 (50.6)	2,529 (47.0)	996 (50.4)	<0.001
Fruit consumption almost every day	15,768 (39.7)	2,219 (43.8)	5,357 (42.9)	5,674 (38.4)	1,814 (33.7)	704 (35.6)	<0.001
Miso soup consumption almost every day	22,226 (56.0)	3,260 (64.3)	7,793 (62.4)	7,749 (52.5)	2,476 (46.0)	948 (48.0)	<0.001
Pickled vegetable consumption almost every day	23,645 (59.6)	3,053 (60.2)	7,763 (62.1)	8,569 (58.1)	3,082 (57.3)	1,178 (59.6)	<0.001
Black tea consumption ≥1 cups/day	2,300 (5.8)	272 (5.4)	673 (5.4)	912 (6.2)	310 (5.8)	133 (6.7)	<0.001
Green tea consumption ≥1 cups/day	28,079 (70.8)	3,567 (70.3)	9,362 (74.9)	10,227 (69.3)	3,631 (67.5)	1,292 (65.4)	<0.001
Employed	28,437 (71.7)	3,595 (70.9)	8,816 (70.5)	10,734 (72.7)	3,964 (73.7)	1,328 (67.2)	<0.001
National health insurance	23,598 (59.5)	3,395 (66.9)	8,085 (64.7)	8,365 (56.7)	2,683 (49.9)	1,070 (54.1)	<0.001

(**Table 1** continued the next page.)

	Total	Never	Sometimes	1–2 cups/day	3–4 cups/day	≥5 cups/day	P-value
Women	43,124	(n=7,772)	(n=16,148)	(n=14,608)	(n=3,351)	(n=1,245)	
Age (years)	54 (46–62)	60 (52–69)	55 (48–63)	51 (45–58)	48 (43–55)	49 (44–57)	<0.001
Prefectures							<0.001
Miyagi	11,590 (26.9)	2,743 (35.3)	5,075 (31.4)	2,981 (20.4)	499 (14.9)	292 (23.5)	
Aichi	15,164 (35.2)	2,444 (31.4)	5,912 (36.6)	5,271 (36.1)	1,183 (35.3)	354 (28.4)	
Osaka	16,370 (38.0)	2,585 (33.3)	5,161 (32.0)	6,356 (43.5)	1,669 (49.8)	599 (48.1)	
Areas							<0.001
Rural	18,182 (42.2)	3,648 (46.9)	6,804 (42.1)	5,822 (39.9)	1,437 (42.9)	471 (37.8)	
Urban	24,942 (57.8)	4,124 (53.1)	9,344 (57.9)	8,786 (60.1)	1,914 (57.1)	774 (62.2)	
BMI (kg/m²)	22.2 (20.4–24.4)	22.2 (20.0–24.4)	22.4 (20.5–24.7)	22.2 (20.4–24.2)	22.1 (20.3–24.0)	22.2 (20.3–24.2)	<0.001
Current smoker	4,744 (11.0)	637 (8.2)	1,189 (7.4)	1,905 (13.0)	693 (20.7)	320 (25.7)	<0.001
Current drinker	2,552 (5.9)	365 (4.7)	731 (4.5)	1,029 (7.0)	312 (9.3)	115 (9.2)	<0.001
Rice consumption ≥3 bowls/day	25,722 (59.6)	4,957 (63.8)	10,189 (63.1)	8,157 (55.8)	1,785 (53.3)	634 (50.9)	<0.001
Bread consumption almost every day	14,528 (33.7)	1,576 (20.3)	3,742 (23.2)	6,966 (47.7)	1,595 (47.6)	649 (52.1)	<0.001
Meat consumption almost every day	6,823 (15.8)	848 (10.9)	2,372 (14.7)	2,640 (18.1)	688 (20.5)	275 (22.1)	<0.001
Fish consumption almost every day	10,052 (23.3)	2,029 (26.1)	4,058 (25.1)	3,016 (20.6)	681 (20.3)	268 (21.5)	<0.001
Egg consumption almost every day	12,762 (29.6)	2,066 (26.6)	4,645 (28.8)	4,488 (30.7)	1,116 (33.3)	447 (35.9)	<0.001
Milk consumption almost every day	14,170 (32.9)	2,609 (33.6)	5,317 (32.9)	4,767 (32.6)	1,042 (31.1)	435 (34.9)	<0.001
Green and yellow vegetable consumption almost every day	20,341 (47.2)	4,004 (51.5)	7,900 (48.9)	6,488 (44.4)	1,403 (41.9)	546 (43.9)	<0.001
Non-green and non-yellow vegetable consumption almost every day	26,180 (60.7)	4,902 (63.1)	10,108 (62.6)	8,597 (58.9)	1,862 (55.6)	711 (57.1)	<0.001
Fruit consumption almost every day	25,487 (59.1)	4,844 (62.3)	9,958 (61.7)	8,331 (57.0)	1,686 (50.3)	668 (53.7)	<0.001
Miso soup consumption almost every day	22,847 (53.0)	4,585 (59.0)	9,416 (58.3)	6,865 (47.0)	1,416 (42.3)	565 (45.4)	<0.001
Pickled vegetable consumption almost every day	27,400 (63.5)	4,934 (63.5)	10,507 (65.1)	9,163 (62.7)	2,000 (59.7)	796 (63.9)	<0.001
Black tea consumption ≥1cups/day	3,110 (7.2)	491 (6.3)	1,224 (7.6)	1,043 (7.1)	239 (7.1)	113 (9.1)	<0.001
Green tea consumption ≥1cups/day	31,991 (74.2)	5,887 (75.7)	12,651 (78.3)	10,350 (70.9)	2,268 (67.7)	835 (67.1)	<0.001
Employed	19,904 (46.2)	3,323 (42.8)	7,091 (43.9)	7,184 (49.2)	1,748 (52.2)	558 (44.8)	<0.001
National health insurance	26,546 (61.6)	5,172 (66.5)	10,191 (63.1)	8,611 (58.9)	1,818 (54.3)	754 (60.6)	<0.001

Data given as n (%) or median (IQR). BMI, body mass index.

The period of time for which participants were asked about the consumption of coffee related to the last few months.

Endpoint

The main outcomes were all-cause mortality and cardiovascular mortality (such as heart disease and cerebrovascular disease). We used the International Classification of Diseases 9th version (ICD-9) in 1983–1994, and/or the 10th version (ICD-10) in 1995–2000 to classify the causes of death as follows: heart disease (ICD-9, 390–398, 401–404, 410–429, and 440–448; ICD-10, I00–I13 and I20–I51) and cerebrovascular disease (ICD-9, 430–438; ICD-10, I60–69).[1,24]

Statistical Analysis

In this study, we conducted analyses by gender. Chi-squared test was used to compare the baseline characteristics by coffee consumption categories. When mortality rates were calculated, person-years of follow-up for mortality were reported from the date of the baseline survey to the following dates, whichever occurred first: end of follow-up; date of death; or date of moving out of the study area. The

Table 2. Coffee Consumption Frequency and All-Cause and Cardiovascular Mortality

	Never	Sometimes		1–2 cups/day		3–4 cups/day		≥5 cups/day		P for trend
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	
Men										
All-cause mortality										
Cases (n=7,955), n	1,520	2,856		2,529		741		309		
Person-years (n=461,700), n	56,932	145,657		172,737		63,304		23,069		
Model 1 adjusted HR (95% CI)	Ref.	0.76 (0.71–0.81)	<0.001	0.72 (0.67–0.77)	<0.001	0.71 (0.65–0.78)	<0.001	0.73 (0.65–0.83)	<0.001	<0.001
Model 2 adjusted HR (95% CI)	Ref.	0.85 (0.80–0.92)	<0.001	0.76 (0.71–0.82)	<0.001	0.74 (0.67–0.81)	<0.001	0.73 (0.64–0.83)	<0.001	<0.001
Heart disease										
Cases (n=1,418), n	245	523		455		131		64		
Person-years (n=461,700), n	56,932	145,657		172,737		63,304		23,069		
Model 1 adjusted HR (95% CI)	Ref.	0.87 (0.75–1.02)	0.083	0.86 (0.74–1.01)	0.067	0.90 (0.72–1.11)	0.318	1.05 (0.79–1.38)	0.754	0.661
Model 2 adjusted HR (95% CI)	Ref.	1.04 (0.88–1.24)	0.621	0.98 (0.82–1.17)	0.811	0.95 (0.75–1.21)	0.700	1.11 (0.83–1.49)	0.489	0.874
Cerebrovascular disease										
Cases (n=973), n	234	375		272		66		26		
Person-years (n=461,700), n	56,932	145,657		172,737		63,304		23,069		
Model 1 adjusted HR (95% CI)	Ref.	0.67 (0.57–0.79)	<0.001	0.58 (0.48–0.69)	<0.001	0.50 (0.38–0.66)	<0.001	0.46 (0.31–0.70)	<0.001	<0.001
Model 2 adjusted HR (95% CI)	Ref.	0.82 (0.68–0.98)	0.033	0.68 (0.55–0.84)	<0.001	0.60 (0.44–0.81)	0.001	0.54 (0.35–0.83)	0.005	<0.001
Women										
All-cause mortality										
Cases (n=5,275), n	1,696	2,012		1,259		205		103		
Person-years (n=530,029), n	91,386	198,576		182,891		41,818		15,359		
Model 1 adjusted HR (95% CI)	Ref.	0.80 (0.75–0.85)	<0.001	0.75 (0.70–0.81)	<0.001	0.70 (0.60–0.81)	<0.001	0.81 (0.66–0.99)	0.041	<0.001
Model 2 adjusted HR (95% CI)	Ref.	0.91 (0.84–0.98)	0.012	0.82 (0.75–0.90)	<0.001	0.73 (0.63–0.86)	<0.001	0.83 (0.68–1.02)	0.083	<0.001
Heart disease										
Cases (n=1,056), n	378	391		226		34		27		
Person-years (n=530,029), n	91,386	198,576		182,891		41,818		15,359		
Model 1 adjusted HR (95% CI)	Ref.	0.74 (0.64–0.85)	<0.001	0.68 (0.58–0.81)	<0.001	0.64 (0.45–0.91)	0.014	1.11 (0.75–1.65)	0.589	0.001
Model 2 adjusted HR (95% CI)	Ref.	0.83 (0.70–0.98)	0.026	0.74 (0.60–0.90)	0.002	0.66 (0.45–0.96)	0.028	1.14 (0.75–1.73)	0.528	0.030
Cerebrovascular disease										
Cases (n=857), n	318	322		172		26		19		
Person-years (n=530,029), n	91,386	198,576		182,891		41,818		15,359		
Model 1 adjusted HR (95% CI)	Ref.	0.77 (0.65–0.90)	0.001	0.71 (0.58–0.86)	<0.001	0.65 (0.44–0.98)	0.041	1.06 (0.66–1.68)	0.819	0.003
Model 2 adjusted HR (95% CI)	Ref.	0.97 (0.81–1.16)	0.711	0.93 (0.74–1.16)	0.505	0.84 (0.55–1.29)	0.429	1.33 (0.82–2.18)	0.253	0.858

Model 1, adjusted for age group, prefecture, area. Model 2, adjusted for age group, prefecture, area, history of hypertension, history of diabetes mellitus, history of stroke, history of heart disease, body mass index, smoking status, alcohol drinking, type of job, type of insurance, rice consumption, bread consumption, meat consumption, fish consumption, egg consumption, milk consumption, green and yellow vegetable consumption, non-green and non-yellow vegetable consumption, fruit consumption, miso soup consumption, pickled vegetable, black tea consumption, green tea consumption.

association between coffee consumption and risk of all-cause and of cardiovascular mortality was estimated using multivariable Cox proportional hazard regression modeling and reported as hazard ratios (HR) and 95% CI. We treated categorical variables as dummy ones in all regression models.

The model was adjusted for the following potential confounders based on previous studies, which included lifestyles, past history, and socioeconomic status:[1,2,18,19,25,26] age category (40–49, 50–59, 60–69, and 70–79 years), prefecture (Miyagi, Aichi, and Osaka Prefectures), area (urban or rural), and body mass index (BMI; men, 14.02–20.19, 20.20–21.79, 21.80–23.14, 23.15–24.79, 24.80–39.76 kg/m^2, or unknown; women, 14.02–19.99, 20.00–21.49, 21.50–23.06, 23.07–24.99, 25.00–40.00 kg/m^2, or unknown). Other confounders were smoking status (never, past, current [0–19 pack-year; 20–39 pack-year; ≥40 pack-year], or unknown) and frequency of alcohol consumption (never, past, occupational or almost every day, or unknown). Consumption of food items such as bread, meat, eggs, milk, fish, green and yellow vegetables, non-green and yellow vegetables, fruit, picked vegetables, and miso soup were categorized as: almost never, 1–2 times/month; 1–2 times/week; 3–4 times/week; almost every day; or unknown). Other confounders included beverages such as green and black tea (almost never; sometimes; 1–2 cups/day; 3–4 cups/day; ≥5 cups/day; or unknown) and rice consumption (0–1 cup/day; 2 cups/day; 3 cups/day; 4 cups/day; 5 cups/day; 6–25 cups/day; or unknown). Types of job were categorized as clerical personnel; sales personnel; agricultural, forestry and fisheries personnel; professional technical and civil personnel; managerial personnel; construction personnel; personnel in transport and communications; craftsman; personnel in security service; production process personnel; laborers; unemployed personnel; or unknown. Social insurance included national health insurance/government/union-managed health insurance/mutual aid associations' health insurance, or unknown. Medical history for conditions such as hypertension, diabetes, stroke, and heart disease were categorized as current, past, never, or unknown. To evaluate for reverse causation, we estimated the risk of mortality from all causes excluding subjects who died in the 3 years from the baseline. In addition, subgroup analysis by smoking status (current or never) was also carried out using multivariable Cox proportional hazard modeling for risks from all causes and cardiovascular disease, to assess for the effect of residual confounding and/or effect modification by smoking. The effect modification was evaluated using interaction P-values between the smoking statuses. Furthermore, we conducted subgroup analyses for age group, area, and prefecture. Using the HR in full adjusted models, the heterogeneity between prefectures (Miyagi, Aichi, Osaka) or areas (rural, urban) by each sex and each outcome were assessed using the Q test and I2 statistic based on a previous study.[8] The level of significance equal to 0.10 was used for the Q test. The I^2 statistic represents the amount of total variation that could be attributed to heterogeneity. I^2 25%, 25–50%, 50–75%, and >75% indicated no, small, moderate, and significant heterogeneity, respectively.[8] Statistical analysis was conducted using STATA version 13 MP (Stata, College Station, TX, USA). All P-values were 2-sided and the significance level was set at P<0.05.

Results

Table 1 lists the subject baseline characteristics by coffee consumption frequency and by gender. Compared with the never coffee drinkers (in men), those who consumed high amounts of coffee were more likely to be young, current smokers, eats foods such as bread and meat; less likely to be current drinkers; eats foods such as rice, fish, green and yellow vegetables; non-green and non-yellow vegetables; and miso soup; as well as drink beverages (such as milk and green tea). Women also had similar trends.

The adjusted HR of mortality from all causes and cardiovascular diseases by coffee consumption frequency and gender are noted in **Table 2**. Higher coffee consumption frequency was associated with lower risk of all-cause mortality in men (adjusted HR for ≥5cups/day vs. never, 0.73; 95% CI: 0.64–0.83) and marginally lower risk in women (adjusted HR, 0.83; 95% CI: 0.68–1.03). Furthermore, increasing coffee consumption frequency was also associated with all-cause mortality in both genders (P for trend<0.001), cerebrovascular disease mortality in men (P for trend<0.001), and heart disease mortality in women (P for trend=0.031).

The adjusted HR between coffee consumption frequency and each mortality outcome by gender and smoking status are shown in **Table 3**. In female non-smokers, increasing coffee consumption frequency was also associated with all-cause mortality (P for trend<0.001) and heart disease mortality (P for trend=0.014). No significant association was observed, however, between increasing coffee consumption and all-cause mortality and cause-specific mortality in non-smoker men. In contrast, in current smokers, increasing coffee consumption frequency was associated with all-cause mortality in both genders (men, P for trend<0.001; women, P for trend=0.019), and with cerebrovascular disease in men (P for trend=0.001). In the subgroup analyses, some results did not show statistical significance because of smaller sample size, but did have similar trends to the main results (**Supplementary Table 2**). In addition, we evaluated the heterogeneity between prefectures or areas by each sex and each outcome using Q test and I^2 statistic. The I^2 and P-values of each outcome for the highest vs. lowest category of coffee consumption were 0% and >0.10. Some Q test and I^2 statistics, however, showed small heterogeneity between prefectures and moderate heterogeneity between areas. As for areas, the I^2 and P-value of heart disease death were 48% and 0.165 in men, and those of cerebrovascular disease death were 46% and 0.173 in women (**Supplementary Table 3**).

Discussion

In the Three-Prefecture Cohort Study, the risk of all-cause mortality reduced with increasing coffee consumption frequency in men and women. In addition, the risk of cerebrovascular disease mortality in men and heart disease mortality in women decreased with increasing coffee consumption frequency. In the subgroup analysis, in non-smoker women, increasing coffee consumption frequency was also associated with all-cause mortality and heart disease mortality. In current-smokers, increasing coffee consumption frequency was also associated with all-cause mortality in both genders, and with cerebrovascular disease in men. The present study, showing an inverse association between coffee consumption frequency and

Table 3. Coffee Consumption Frequency and Mortality Outcome by Gender and Smoking Status

	Never	Sometimes		1–2 cups/day		3–4 cups/day		≥5 cups/day		P for trend	P for interaction
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value		
Men											
All-cause mortality (Smoking status)											
Never smoker											
Cases (n=963), n	281	405		208		47		22			
Model 1 adjusted HR (95% CI)	Ref.	0.72 (0.62–0.84)	<0.001	0.72 (0.60–0.86)	<0.001	0.83 (0.60–1.13)	0.238	0.63 (0.41–0.97)	0.036	0.002	
Model 2 adjusted HR (95% CI)	Ref.	0.85 (0.71–1.01)	0.072	0.83 (0.67–1.03)	0.084	0.94 (0.67–1.32)	0.732	0.73 (0.46–1.15)	0.174	0.147	
Current smoker											
Cases (n=4,832), n	754	1,568		1,695		577		238			
Model 1 adjusted HR (95% CI)	Ref.	0.77 (0.70–0.84)	<0.001	0.69 (0.63–0.75)	<0.001	0.66 (0.59–0.74)	<0.001	0.67 (0.58–0.78)	<0.001	<0.001	
Model 2 adjusted HR (95% CI)	Ref.	0.86 (0.78–0.95)	0.002	0.75 (0.68–0.83)	<0.001	0.73 (0.65–0.82)	<0.001	0.70 (0.60–0.82)	<0.001	<0.001	0.757
Heart disease (Smoking status)											
Never smoker											
Cases (n=172), n	51	75		36		9		1			
Model 1 adjusted HR (95% CI)	Ref.	0.74 (0.52–1.06)	0.104	0.75 (0.49–1.17)	0.206	1.03 (0.50–2.11)	0.946	0.16 (0.02–1.19)	0.073	0.095	
Model 2 adjusted HR (95% CI)	Ref.	1.05 (0.68–1.62)	0.825	0.97 (0.58–1.63)	0.910	1.12 (0.51–2.46)	0.774	0.19 (0.03–1.50)	0.116	0.409	
Current smoker											
Cases (n=848), n	125	268		299		104		52			
Model 1 adjusted HR (95% CI)	Ref.	0.80 (0.65–0.99)	0.040	0.79 (0.63–0.97)	0.027	0.82 (0.63–1.07)	0.140	1.00 (0.72–1.39)	0.999	0.639	
Model 2 adjusted HR (95% CI)	Ref.	0.91 (0.72–1.15)	0.415	0.86 (0.67–1.10)	0.224	0.88 (0.66–1.18)	0.400	1.06 (0.74–1.50)	0.765	0.859	0.420
Cerebrovascular disease (Smoking status)											
Never smoker											
Cases (n=150), n	54	59		31		4		2			
Model 1 adjusted HR (95% CI)	Ref.	0.56 (0.39–0.81)	0.002	0.66 (0.42–1.03)	0.067	0.45 (0.16–1.24)	0.122	0.33 (0.08–1.34)	0.120	0.010	
Model 2 adjusted HR (95% CI)	Ref.	0.70 (0.44–1.12)	0.136	0.89 (0.51–1.55)	0.678	0.49 (0.16–1.51)	0.214	0.43 (0.10–1.92)	0.270	0.237	
Current smoker											
Cases (n=554), n	101	208		176		50		19			
Model 1 adjusted HR (95% CI)	Ref.	0.78 (0.62–1.00)	0.046	0.61 (0.47–0.78)	<0.001	0.51 (0.36–0.72)	<0.001	0.47 (0.28–0.76)	0.002	<0.001	
Model 2 adjusted HR (95% CI)	Ref.	0.95 (0.73–1.25)	0.720	0.75 (0.56–1.00)	0.050	0.67 (0.46–0.97)	0.036	0.58 (0.34–0.97)	0.039	0.002	0.783

(**Table 3** continued the next page.)

	Never	Sometimes		1–2 cups/day		3–4 cups/day		≥5 cups/day		P for trend	P for interaction
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value		
Women											
All-cause mortality (Smoking status)											
Never smoker											
Cases (n=3,522), n	1,256	1,345		747		118		56			
Model 1 adjusted HR (95% CI)	Ref.	0.77 (0.71–0.84)	<0.001	0.69 (0.63–0.76)	<0.001	0.67 (0.55–0.81)	<0.001	0.80 (0.61–1.05)	0.108	<0.001	
Model 2 adjusted HR (95% CI)	Ref.	0.89 (0.81–0.97)	0.010	0.80 (0.72–0.90)	<0.001	0.77 (0.63–0.94)	0.011	0.94 (0.71–1.23)	0.638	<0.001	
Current smoker											
Cases (n=810), n	190	253		277		58		32			
Model 1 adjusted HR (95% CI)	Ref.	0.90 (0.74–1.09)	0.274	0.81 (0.67–0.98)	0.031	0.67 (0.49–0.91)	0.010	0.82 (0.56–1.20)	0.304	0.009	
Model 2 adjusted HR (95% CI)	Ref.	0.99 (0.79–1.23)	0.898	0.84 (0.67–1.06)	0.143	0.66 (0.48–0.92)	0.015	0.75 (0.50–1.13)	0.166	0.008	0.785
Heart disease (Smoking status)											
Never smoker											
Cases (n=688), n	275	267		122		13		11			
Model 1 adjusted HR (95% CI)	Ref.	0.75 (0.64–0.90)	0.001	0.60 (0.48–0.75)	<0.001	0.42 (0.24–0.74)	0.003	0.84 (0.46–1.54)	0.570	<0.001	
Model 2 adjusted HR (95% CI)	Ref.	0.85 (0.70–1.04)	0.112	0.72 (0.56–0.93)	0.011	0.51 (0.29–0.91)	0.023	1.06 (0.56–1.98)	0.865	0.013	
Current smoker											
Cases (n=193), n	48	55		63		16		11			
Model 1 adjusted HR (95% CI)	Ref.	0.79 (0.54–1.18)	0.250	0.80 (0.55–1.18)	0.270	0.92 (0.52–1.65)	0.786	1.50 (0.77–2.93)	0.236	0.780	
Model 2 adjusted HR (95% CI)	Ref.	0.73 (0.46–1.16)	0.185	0.67 (0.41–1.09)	0.106	0.86 (0.45–1.67)	0.661	1.10 (0.52–2.34)	0.802	0.860	0.146
Cerebrovascular disease (Smoking status)											
Never smoker											
Cases (n=565), n	236	212		98		11		8			
Model 1 adjusted HR (95% CI)	Ref.	0.73 (0.61–0.89)	0.001	0.64 (0.50–0.82)	<0.001	0.48 (0.26–0.88)	0.018	0.83 (0.41–1.69)	0.611	<0.001	
Model 2 adjusted HR (95% CI)	Ref.	0.90 (0.72–1.12)	0.340	0.84 (0.63–1.11)	0.220	0.63 (0.33–1.18)	0.147	1.11 (0.53–2.30)	0.785	0.204	
Current smoker											
Cases (n=127), n	32	43		35		7		10			
Model 1 adjusted HR (95% CI)	Ref.	1.01 (0.63–1.60)	0.971	0.75 (0.45–1.23)	0.252	0.61 (0.26–1.40)	0.241	2.07 (0.99–4.32)	0.052	0.963	
Model 2 adjusted HR (95% CI)	Ref.	1.26 (0.72–2.19)	0.413	1.03 (0.56–1.90)	0.918	0.83 (0.33–2.09)	0.698	2.98 (1.25–7.09)	0.014	0.264	0.116

Model 1, adjusted for age group, sex, region. Model 2, adjusted for age group, prefecture, area, history of hypertension, history of diabetes mellitus, history of stroke, history of heart disease, body mass index, smoking status, alcohol drinking, type of job, type of insurance, rice consumption, bread consumption, meat consumption, fish consumption, egg consumption, milk consumption, green and yellow vegetable consumption, non-green and non-yellow vegetable consumption, fruit consumption, miso soup consumption, pickled vegetable, black tea consumption, green tea consumption.

all-cause mortality, and cardiovascular-related disease mortality, provides useful information for preventing mortality in the general Japanese population. From the present results, coffee drinking did not increase all-cause death and cardiovascular-related disease mortality in the Japanese population, and drinking coffee routinely might be considered for their prevention.

In the present study the risk of all-cause mortality decreased in both genders, similarly to previous cohort studies,[1,2,14–17] and meta-analyses.[6,7] In Japan, higher coffee consumption frequency was significantly associated with lower risk of all-cause mortality in both genders, in the Japan Public Health Center (JPHC) cohort (adjusted HR for ≥5 cups/day vs. never, 0.80; 95% CI: 0.68–0.95).[1] In men, in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study) a significant association was also noted (adjusted HR for ≥4 cups/day vs. <1 cup/day, 0.80; 95% CI: 0.68–0.95).[2] No association was seen, however, in women in the JACC study (0.89; 95% CI: 0.66–1.20).[2] The present results were similar to these results, especially the JACC study, and reinforced the inverse association between coffee consumption and all-cause mortality in Japanese people. Coffee contains numerous biologically active compounds, which include caffeine, phenolic acids, and potassium.[3,4] Thus, complex mechanisms have been suggested to explain the potential inverse association between coffee and all-cause mortality.

The risk of mortality due to cerebrovascular disease in men and to heart disease in women significantly decreased with increasing coffee consumption frequency, and these results reinforced findings of previous studies.[1,14–16,24] In Japan, higher coffee consumption frequency was associated with a lower risk of death from heart disease (P for trend=0.004) and of cerebrovascular death (P for trend<0.001) in both genders in the JPHC study.[1] In addition, the JACC study reported that higher coffee consumption frequency was associated with lower risk of stroke death in men (P for trend=0.009), but no significantly lower risk of ischemic heart disease death was seen in women (P for trend=0.409).[19] The present results are similar to the JPHC study, but different from the JACC study. The different definitions of the causes of death between these studies, including ours, might explain the difference in results. The reason for the discrepancy in results between men and women concerning the effect of coffee consumption on death (from heart disease and cerebrovascular disease) in the present study is unknown. The potential mechanism for decreasing the risk of cardiovascular-related death, however, could be partially explained by the major phenolic compound in coffee (e.g., chlorogenic acid), which is known to attenuate the rate of glucose absorption[1,27] and lower blood pressure.[1,28] Moreover, as suggested, caffeine improves[1,29] and promotes the repair of endothelial function.[1,30] In addition, antioxidant actions by coffee consumption may inhibit inflammation, thereby decreasing the risk of cardiovascular-related death.[16,31]

We conducted a subgroup analysis according to smoking status to determine any residual confounding, because coffee consumption frequency was higher in current smokers than in non-smokers. If smoking status were a residual confounder, the risk reduction with coffee consumption would be greater in non-smokers than in smokers. Subgroup analysis, however, indicated the same tendency in both current smokers and non-smokers; this suggests the robustness of the associations,[1] which would not be residual confounding. In contrast, in the recent meta-analysis on the association between coffee consumption and all-cause or cause-specific mortality by smoking status, the inverse effect of coffee intake in non-smokers was stronger than in current smokers.[32] Thus, in Japanese people, the conclusion regarding the effect of coffee consumption on these mortalities by smoking status would also need to be confirmed by further meta-analysis and pooled analysis using large-scale cohorts, including the present results.

Study Limitations

This study has several limitations. First, the questionnaire used for coffee consumption frequency was not common across the 3 prefectures, and could have resulted in higher estimated amounts of coffee consumption because its categories were combined. Therefore, we assessed for any difference in the risk between prefectures (data not shown), but this was small. Second, the self-administered questionnaire on coffee consumption frequency was conducted only once. The frequency, however, might have changed during the follow-up period. For example, given that the mean age in non-coffee drinkers was higher than in coffee drinkers, the proportion of subjects who answered no to drinking coffee might have increased during follow-up. Therefore, the reduction effect on the risk of mortality by coffee consumption might be underestimated by the baseline questionnaire. Third, we could not adjust for unknown confounding factors that could affect the relationship between coffee consumption and mortality. Indeed, some analyses reported moderate heterogeneity between areas, and several factors may, therefore, explain unmeasured differences across areas. Finally, a total of 14,233 participants without information on coffee consumption were removed from the study, which might have an influence on the results as a possible selection bias.

Conclusions

In this Japanese population, increasing coffee consumption led to a decrease in the risk of all-cause and cardiovascular mortality in men and/or women.

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Disclosures

The authors declare no conflicts of interest.

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Supplementary Files

Please find supplementary file(s);
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