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Coffee consumption and mortality in Japanese men and women: A pooled analysis of eight population-based cohort studies in Japan (Japan Cohort Consortium)

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ABSTRACT

Coffee consumption is increasing globally. We aimed to assess the effect of coffee consumption on the risk of all-cause and cause-specific mortality in a pooled analysis of eight population-based cohort studies in Japan (Japan Cohort Consortium). Data came from eight Japanese cohort studies (144,750 men and 168,631 women). During a mean follow-up time of 17 years, 52,943 deaths occurred. More specifically, 19,495 cancer deaths, 7321 deaths due to heart disease, 6387 cerebrovascular, 3490 respiratory disease and 3382 injuries and accidents. A random effects model was applied to obtain pooled hazard ratios (HRs) and 95% confidence intervals (95%CIs). In both sexes, coffee consumption up to 5 cups/day was overall protective in relation to all-cause mortality, with the association attenuating in the highest category of coffee consumption (≥5 cups/day). In men, a similar inverse association was observed for major causes of mortality except cancer. In women, coffee consumption decreased the risk for mortality due to heart disease in the 1–2 cups/day category, but increased the risk in the ≥5 cups/day category. Coffee consumption was not associated with cancer in both sexes. Results were similar among male current smokers and female never-smokers. Based on available data, this pooled analysis suggests that coffee consumption under five cups per day may be beneficial for reducing the risk of mortality due to major causes.

Abbreviations: JPHC-I, the Japan Public Health Center-based Prospective Study, Cohort I; JPHC-II, the Japan Public Health Center-Based Prospective Study, Cohort II; JACC, the Japan Collaborative Cohort Study; MIYAGI, the Miyagi Cohort Study; OHSAKI, the Ohsaki National Health Insurance Cohort Study; 3-pref MIYAGI, the Three Prefecture Study–Miyagi portion; 3-pref AICHI, the Three Prefecture Study–Aichi portion; 3-pref OSAKA, the Three Prefecture Study–Osaka portion

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1. Introduction

Coffee is widely consumed in Japan, with nearly 50% of Japanese adults daily consuming coffee (Iso et al., 2006). Globally coffee consumption is also increasing (Food and Agriculture Organization, 2015). The health benefits and risks of drinking coffee have been the subject of extensive research over the past decades. An increasing number of epidemiological studies in various populations have suggested an inverse association between coffee and all-cause and cause-specific mortality (Je and Giovannucci, 2014; Loftfield et al., 2018; Park et al., 2017; Freedman et al., 2012; Grosso et al., 2016). A 2014 meta-analysis, including 20 studies from predominantly Western countries, suggested an overall 14% decreased risk of all-cause mortality in the high versus low category of coffee consumption (Je and Giovannucci, 2014). Three Japanese cohorts were included in the meta-analysis: the Miyagi Cohort Study (Sugiyama et al., 2010), the Japan Collaborative Cohort Study (Tamakoshi et al., 2011) and a cohort of a rural Japanese population (Iwai et al., 2002). The summary pooled relative risk (RR) of total mortality for high versus low/no coffee consumption was 0.82 (95%CI, 0.73–0.92) for the three Japanese studies (Je and Giovannucci, 2014). The association appeared to be slightly stronger in the European and Japanese studies compared to those conducted in the USA. Recently, the large UK Biobank cohort and Multiethnic Cohort (MEC) in the United States corroborated the protective effects of coffee on all-cause mortality, showing a 6–12% and 12–18% decreased risk for all-cause mortality, respectively (Loftfield et al., 2018; Park et al., 2017).

Regarding cause-specific mortality, previous studies present conflicting results on mortality from cardiovascular disease (Loftfield et al., 2018; Freedman et al., 2012; Liu et al., 2013; Lopez-Garcia et al., 2011) and no association with total cancer mortality (Loftfield et al., 2018; Freedman et al., 2012; Sugiyama et al., 2010; Tamakoshi et al., 2011; Lopez-Garcia et al., 2008). A prospective American cohort study found that in men moderate consumption of coffee was protective of death due to heart disease, respiratory failure, and stroke (Freedman et al., 2012). A similar pattern was found among women except for stroke mortality and with the addition of mortality due to injuries and accidents (Freedman et al., 2012).

Although several Japanese cohort studies have reported a protective association between habitual coffee drinking and risk of all-cause mortality (Sugiyama et al., 2010; Tamakoshi et al., 2011; Saito et al., 2015), findings on cause-specific outcomes, including cancer, cerebrovascular, and heart disease have been inconsistent and inconclusive. In this pooled analysis we aimed to assess the effect of coffee consumption on the risk of all-cause and cause-specific mortality using eight population-based cohort studies in Japan.

2. Methods

2.1. Study population

Since 2006 the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan has been conducting pooled analyses (Sasazuki et al., 2018), seeking to assess associations between lifestyle and cancer as well as other causes of mortality. For the present analysis, inclusion criteria were defined a priori to ensure comparability and quality of data: Japanese population-based cohort studies with > 30,000 enrollees initiated between mid-1980s and mid-1990s; using a validated questionnaire to obtain baseline data on coffee drinking; and that collected data on cause-specific mortality during a follow-up period. As a result, eight Japanese population-based cohort studies were included: 1) the Japan Public Health Center-based Prospective Study-I (JPHC-I) (Tsugane and Sawada, 2014), 2) the Japan Public Health Center-based Prospective Study-II (JPHC-II) (Tsugane and Sawada, 2014), 3) the Japan Collaborative Cohort Study (JACC) (Tamakoshi et al., 2005), 4) the Miyagi Cohort Study (MIYAGI-I) (Tsuji et al., 2004), 5) the Ohsaki National Health Insurance Cohort Study (OHSAKI) (Tsuji et al., 2003), 6) the Three Prefecture Cohort Study–-Miyagi portion (3-pref MIYAGI) (Sado et al., 2017), 7) the Three Prefecture Cohort Study–Aichi portion (3-pref AICHI) (Sado et al., 2017), and 8) the Three Prefecture Cohort Study–Osaka portion (3-pref OSAKA) (Sado et al., 2017). We excluded participants with missing information on sex, age, area (only for JPHC and JACC studies), or coffee drinking and those with a history of cancer, stroke, and myocardial infarction at baseline. Studies were approved by the relevant institutional ethical review boards. Findings on the association between coffee consumption and overall and cause-specific mortality have already been reported from the JPHC (Saito et al., 2015), JACC (Tamakoshi et al., 2011) and MIYAGI (Sugiyama et al., 2010) studies. For this study, we reanalyzed the coffee-mortality associations using updated datasets from the original studies.

2.2. Exposure assessment

The baseline questionnaires in each cohort included questions on the average frequency and quantity of coffee intake. We classified coffee consumption as < 1, 1–2, 3–4, and ≥5 cups per day. We also combined the categories of 3–4 cups/day and ≥5 cups to ensure sufficient cases for subgroup analyses stratified by smoking status. These coffee exposure categories were selected as they were the most common across all eight cohort studies (Supplement Table 1).

2.3. Case ascertainment

The baseline survey served as the starting point for follow-up: (JPHC I: 1990, JPHC II: 1993–1994, JACC: 1988–1990, MIYAGI: 1990, OHSAKI: 1994, 3-pref MIYAGI: 1984, 3-pref AICHI: 1985, 3-pref OSAKA: 1983). The last follow-up year was the following for each study: JPHC I: 2011, JPHC II: 2011, JACC: 2009, MIYAGI: 2013, OHSAKI: 2008, 3-pref MIYAGI: 1998, 3-pref AICHI: 2000, 3-pref OSAKA: 2000. Under the Family Registration Law in Japan, death certificates are forwarded to the Ministry of Health, Labour and Welfare. This data was used to collect information on cause of death coding according to the International Classification of Diseases and Health Related Problems, Tenth Revision (ICD-10) (World Health Organization, 1992). The main study outcome was all-cause mortality. We also assessed risk for the five leading causes of death in Japan (Liu et al., 2013): cancer (C00–C97), heart disease (I20–I52), cerebrovascular disease (I60–I69), respiratory disease (J10–J18 and J40–J47), and injuries and accidents (V01–X59, X60–X84, X85–Y09, and Y85–Y86).

2.4. Statistical analysis

The date of the baseline survey for each study was used to calculate person-years of follow-up until the date of death, or end of follow-up, whichever occurred first. Hazard ratios (HRs) were estimated using a cox proportional hazards model and two-sided 95% CIs for each study, with consumption of coffee < 1 cup per day as the reference category. A pooled HR was estimated using a random effects model, which considered both within- and between-study variation (DerSimonian and Laird, 1986). All analyses were adjusted for age at baseline (years, continuous), area (for JPHC-I, JPHC-II and JACC), smoking status (men: never, former, < 20 cigarettes/day, ≥20 cigarettes/day; women: never, former, current), alcohol intake (men: none (never/former), < 1 times/week, regular (g/d) [< 23, 23 ≤ 46, 46 ≤ 69, 69 ≤ 92, ≥92]; women: none (never/former), < 1 times/week, regular (g/d) [< 23, ≥23]), BMI (< 18.5, 18.5 ≤ 25, 25 ≤ 30, ≥30 (< 14, ≥40 were treated as missing), history of diabetes (yes, no) and history of hypertension (yes, no), and green tea (cups/day). Sensitivity analyses were performed excluding deaths occurring within five years of follow-up. We repeated analyses stratified by smoking status (current, never), for cause-specific outcomes in female non-smokers. Heterogeneity

Table 1
Characteristics of the Japanese cohort studies included in the present pooled analysis.

Study	Initial population	Age range at baseline, years	Follow-up (start-end)	Average follow-up period, years	Number of subjects		Number of deaths		Remarks
					Men	Women	Men	Women	
JPHC-I	Japanese residents of 5 public health center areas in Japan	40–59	1990–2011	20.25	22,597	25,382	4063	2083	
JPHC-II	Japanese residents of 6 public health center areas in Japan	40–69	1993–2011	17.30	27,941	31,415	6299	3622	
JACC	Residents from 45 areas throughout Japan	40–79	1988–2009	16.10	28,258	39,446	15,401	12,009	
MIYAGI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990–2013	20.52	16,874	18,077	4018	2253	Missing all mortality current smoker data for women
OHSAKI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–79	1994–2008	11.66	12,152	13,194	3121	1794	Missing all mortality current smoker data for women
3-pref MIYAGI	Residents of 3 municipalities in Miyagi Prefecture, Japan	40 +	1984–1998	10.98	16,749	18,185	1664	1241	Missing injury and accident data and all mortality current smoker data for women
3-Pref AICHI	Residents of 2 municipalities in Aichi Prefecture, Japan	40–103	1985–2000	11.67	8663	9951	2041	1508	Missing injury and accident data
3-Pref OSAKA	Residents of 4 municipalities in Osaka Prefecture, Japan	40–97	1983–2000	12.56	11,516	12,981	2462	1927	Missing injury and accident data and all mortality current smoker data for women
Total	8 cohorts in Japan				144,750	168,631	39,069	26,437	

Abbreviations: JPHC, The Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study; 3-pref MIYAGI, The Three-Prefecture Cohort Study in Miyagi; 3-pref AICHI, Three-Prefecture Cohort Study in Aichi; OHSAKI, The Ohsaki Cohort Study; 3-pref Osaka, The Three-Prefecture Cohort Study in Osaka.

among studies was tested using Q statistics (DerSimonian and Laird, 1986). STATA Version 14.0 (Stata Corporation, College Station, TX) was used for statistical analyses.

3. Results

This pooled analysis included 144,750 men and 168,631 women. During an average follow-up of 17.3 years, deaths due to the following five major causes were reported: cancer (12,540 men and 6955 women), heart disease (4195 men and 3126 women), cerebrovascular (3487 men and 2900 women), respiratory disease (2049 men and 1441 women) and injuries and accidents (2123 men and 1259 women) (Tables 1–3).

Table 1 presents selected characteristics of the respective populations in each Japanese cohort study. Age of participants at baseline in all cohorts was > 40 years. Baseline surveys were initiated between 1983 and 1994. The total population included 454,235 participants ranging from 31,345 (MIYAGI-II) to 110,585 (JACC). The average response rate of the baseline questionnaire was 87%; the response rate in all included studies was > 80%. The average follow-up time for the present pooled analysis was 17.3 years, and death certificates were used to confirm the outcomes in all included cohorts.

The individual cohort hazard ratios (HR) of all-cause mortality for men and women who consumed 1–2, 3–4, ≥5 (≥3 cups) per day are presented in Supplementary Table 1, with those who consumed < 1 cup/day as the reference.

In the multivariate-adjusted model including the following covariates: age, area (JPHC and JACC), smoking, alcohol intake, body mass index, history of diabetes and blood pressure, and green tea consumption, coffee was overall protective in relation to all-cause mortality in men and women (Tables 2 and 3). The association attenuated in the highest category (≥5 cups of coffee/day) among women. In men, the associations for major causes of mortality except cancer were similar to all-cause mortality. For cerebrovascular disease, the HR for death among men who drank 1–2 cups of coffee per day was 0.84 (95%CI, 0.75–0.95) and 0.73 (95%CI, 0.59–0.90) for those who drank 3–4 cups/day (Table 2). For injuries and accidents, the HR for death among men who consumed 3–4 cups of coffee/day was 0.70 (95% CI, 0.58–0.84) (Table 2). In women, coffee consumption of 1–2 cups/day was associated with 17% decreased risk of cerebrovascular disease {HR = 0.83 (95%CI, 0.73–0.95)} (Table 3). A pattern for respiratory disease was less clear; however, the HR for death among men who drank 1–2 cups/day was 0.84 (95%CI, 0.77–0.93), 0.82 (95%CI, 0.68–0.99) among men who drank 3–4 cup/day (Table 2), and 0.80 (95%CI, 0.69–0.93) among women who drank 1–2 cups/day (Table 3). For heart disease, coffee consumption was protective in the 1–2 cups/day group among women {HR = 0.80 (95%CI, 0.66–0.96)}, but became a risk factor when consumption increased to ≥5 cups/day {HR = 1.47 (95%CI, 1.11–1.95)} (Table 3). Coffee consumption was not associated with cancer mortality in both sexes.

After stratifying by smoking status, results remained similar in current smokers among men for all cause, cerebrovascular disease and injury and accidents mortality risk (Table 2). Among never-smokers, drinking 1–2 cups/day was protective of all-cause mortality in men {HR = 0.87 (95%CI, 0.81–0.94)}. Consuming ≥3 cups of coffee per day was associated with increased risk of death due to respiratory disease among male never-smokers {HR = 1.56 (95%CI, 1.01–2.40)}, but decreased risk was noted among smokers {HR = 0.81 (95%CI, 0.67–0.97)}. This association attenuated in the ≥5 cups/day group. Among female never-smokers, results remained virtually unchanged, except for risk of heart disease among the highest consumer group (≥5 cups/day) (Table 3).

4. Discussion

Our pooled-analysis of eight cohort studies in Japan indicated that

Table 2
Pooled analysis evaluating the effect of coffee consumption and mortality risk in Japanese men.

	Coffee consumption									
	< 1 cup/day	1–2 cups/day		3–4 cups/day		≥ 5 cups/day		≥ 3 cups/day		Heterogeneity[d]	
	HR[a]	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	*P* for trend	%
Total number of subjects											
(*n* = 144,750)	80,925	43,442		15,091		5292		20,383			
No. of subjects (never)	19,398	7621		1771		465		2236			
No. of subjects (current)	38,073	25,391		10,732		4039		14,771			
Person-years	127,100,000	68,036,376		22,791,718		10,141,601		32,933,319			
All mortality											
No. of cases (*n* = 32,085)	21,268	7839		2127		851		2978			
HR1 (model 1[b])	1.00	0.89	0.86, 0.93	0.85	0.81, 0.89	0.90	0.83, 0.96	0.86	0.83, 0.90	< 0.001	99.8
HR2 (model 2[c])	1.00	0.92	0.89, 0.95	0.87	0.83, 0.91	0.94	0.87, 1.01	0.88	0.84, 0.92	< 0.001	99.8
Stratified by smoking status											
No. of cases never	3695	910		171		60		231			
HR3 (model 1) never	1.00	0.87	0.81, 0.94	0.90	0.72, 1.14	0.96	0.79, 1.17	0.95	0.78, 1.15	< 0.001	98.0
No. of cases current	112,67	5128		1642		663		2305			
HR4 (model 1) current	1.00	0.92	0.88, 0.96	0.88	0.82, 0.94	0.91	0.84, 0.99	0.90	0.85, 0.95	< 0.001	99.7
Cancer											
No. of cases (*n* = 12,540)	7939	3275		963		363		1326			
HR1 (model 1[b])	1.00	0.94	0.89, 1.00	0.94	0.87, 1.02	0.95	0.85, 1.05	0.94	0.89, 1.00	< 0.001	99.5
HR2 (model 2[c])	1.00	0.99	0.95, 1.04	0.96	0.89, 1.03	1.00	0.89, 1.13	0.97	0.90, 1.03	< 0.001	99.4
Stratified by smoking status											
No. of cases never	1189	324		63		22		85			
HR3 (model 1) never	1.00	0.89	0.77, 1.01	0.97	0.74, 1.29	1.26	0.82, 1.93	0.95	0.72, 1.25	< 0.001	93.3
No. of cases current	4484	2214		776		293		1069			
HR4 (model 1) current	1.00	0.98	(0.92–1.04)	1.04	0.92, 1.17	0.98	0.88, 1.09	1.02	0.93, 1.11	< 0.001	99.4
Heart disease											
No. of cases (*n* = 4195)	2768	1023		278		126		404			
HR1 (model 1[b])	1.00	0.91	0.85, 0.98	0.89	0.75, 1.05	1.06	0.88, 1.27	0.94	0.84, 1.05	< 0.001	98.5
HR2 (model 2[c])	1.00	0.92	0.85, 1.00	0.87	0.72, 1.04	1.21	0.92, 1.37	0.93	0.82, 1.05	< 0.001	98.2
Stratified by smoking status											
No. of cases never	494	111		23		5		28			
HR3 (model 1) never	1.00	0.86	0.69, 1.06	1.07	0.69, 1.67	0.96	0.39, 2.35	0.94	0.63, 1.41	< 0.001	81.9
No. of cases current	1461	698		204		95		299			
HR4 (model 1) current	1.00	0.98	0.89, 1.08	0.86	0.71, 1.05	1.05	0.85, 1.30	0.91	0.80, 1.04	< 0.001	98.1
Cerebrovascular disease											
No. of cases (*n* = 3487)	2481	770		169		67		236			
HR1 (model 1[b])	1.00	0.84	0.75, 0.95	0.73	0.59, 0.90	0.77	0.51, 1.16	0.73	0.57, 0.94	< 0.001	98.1
HR2 (model 2[c])	1.00	0.86	0.75-0.98	0.81	0.65, 1.01	0.77	0.45, 1.29	0.80	0.61, 1.05	< 0.001	97.6
Stratified by smoking status											
No. of cases never	492	101		17		6		23			
HR3 (model 1) never	1.00	0.87	0.70, 1.09	0.94	0.58, 1.55	1.13	0.49, 2.59	1.48	0.51, 4.27	< 0.001	86.2
No. of cases current	1172	421		109		35		144			
HR4 (model 1) current	1.00	0.81	0.69, 0.95	0.76	0.60, 0.96	0.80	0.51, 1.23	0.76	0.59, 0.98	< 0.001	97.3
Respiratory disease											
No. of cases (*n* = 2895)	2049	637		147		62		209			
HR1 (model 1[b])	1.00	0.84	0.77, 0.93	0.82	0.68, 0.99	0.93	0.72, 1.20	0.83	0.72, 0.97	< 0.001	97.6
HR2 (model 2[c])	1.00	0.87	0.79, 0.96	0.83	0.67, 1.03	0.89	0.67, 1.18	0.86	0.72, 1.02	< 0.001	97.0
Stratified by smoking status											
No. of cases never	347	67		19		5		24			
HR3 (model 1) never	1.00	0.75	0.54, 1.05	1.66	1.02, 2.68	2.50	0.97, 6.46	1.56	1.01, 2.40	< 0.001	80.7
No. of cases current	980	394		92		47		139			
HR4 (model 1) current	1.00	0.92	0.81, 1.04	0.77	0.57, 1.03	0.98	0.73, 1.33	0.81	0.67, 0.97	< 0.001	80.7
Injuries and accidents											
No. of cases (*n* = 2123)	1361	549		141		72		213			
HR1 (model 1[b])	1.00	0.93	0.81, 1.07	0.70	0.58, 0.84	0.84	0.51, 1.41	0.74	0.57, 0.96	< 0.001	98.7
HR2 (model 2[c])	1.00	0.96	0.85, 1.07	0.71	0.53, 0.94	0.82	0.41, 1.62	0.72	0.11, 1.31	< 0.001	98.2
Stratified by smoking status											
No. of cases never	313	95		13		5		18			

(*continued on next page*)

Table 2 (*continued*)

	Coffee consumption										
	< 1 cup/day	1–2 cups/day		3–4 cups/day		≥5 cups/day		≥3 cups/day		Heterogeneity[d]	
	HR[a]	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	*P* for trend	%
HR3 (model 1) never	1.00	0.96	0.70, 1.32	0.70	0.32, 1.50	1.11	0.45, 2.71	0.76	0.43, 1.33	< 0.001	92.0
No. of cases current	833	396		122		59		181			
HR4 (model 1) current	1.00	0.97	0.85, 1.11	0.72	0.56, 0.88	1.01	0.66, 1.51	0.76	0.59, 0.99	< 0.001	98.1

Abbreviations: CI, confidence interval; HR, hazard ratio.
Missing injury and accident data for 3-pref MIYAGI, Aichi and OSAKA.
[a] Cox proportional hazards models were used with random effects.
[b] Model 2: Adjusted for age (years, continuous), area (JPHC and JACC only), smoking status (never, former, < 20 cigarettes/day, ≥20 cigarettes/day), alcohol intake (none (never/former), < 1 times/week, regular (g/d) [< 23, 23 to < 46, 46 to < 69, 69 to < 92, ≥92]), BMI (< 18.5, 18.5 to < 25, 25 to < 30, ≥30 (< 14, ≥40 were treated as missing), history of diabetes (yes, no) and history of hypertension (yes, no), and green tea (cups/day).
[c] Model 3: Model 2 excluding incident cancer cases within 5 years.
[d] Heterogeneity across cohorts.

Table 3
Pooled analysis evaluating the effect of coffee consumption and mortality risk in Japanese women.

	Coffee consumption										
	< 1 cup/day	1-2 cups/day		3-4 cups/day		≥5 cups/day		≥3 cups/day		Heterogeneity[d]	
	HR[a]	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	*P* for trend	%
Total no. of subjects (*n* = 168,631)	101,598	51,887		11,761		3385		15,146			
No. of subjects (never)	85,294	41,806		8643		2111		10,754			
Person-years	155,100,000	78,821,096		16,986,154		6,178,996		23,165,150			
All mortality											
No. of cases (*n* = 20,858)	15,693	4236		663		266		929			
HR1 (model 1[b])	1.00	0.88	0.85, 0.91	0.84	0.77, 0.91	1.00	0.88, 1.27	0.85	0.80, 0.91	< 0.001	99.6
HR2 (model 2[c])	1.00	0.90	0.86, 0.94	0.87	0.80, 0.95	1.07	0.93, 1.22	0.88	0.83, 0.93	< 0.001	99.5
Stratified by smoking status											
No. of cases never	12,630	3109		438		139		577			
HR3 (model 1) never	1.00	0.87	0.84, 0.91	0.87	0.77, 0.97	0.96	0.78, 1.19	0.88	0.78, 0.99	< 0.001	99.4
No. of cases current	631	348		101		54		155			
HR4 (model 1) current	1.00	0.97	0.84, 1.12	0.84	0.67, 1.05	1.04	0.78, 1.39	0.90	0.74, 1.09	< 0.001	98.1
Cancer											
No. of cases (*n* = 6955)	4878	1667		314		96		410			
HR1 (model 1[b])	1.00	0.93	0.88, 0.99	0.95	0.85, 1.07	0.94	0.76, 1.17	0.92	0.85, 1.00	< 0.001	99.0
HR2 (model 2[c])	1.00	0.97	0.90, 1.05	1.04	0.92, 1.17	0.94	0.76, 1.17	0.97	0.89–1.06	< 0.001	98.8
Stratified by smoking status											
No. of cases never	3968	1292		169		123		292			
HR3 (model 1) never	1.00	0.96	0.89, 1.02	0.98	0.85, 1.13	1.07	0.78, 1.47	0.98	0.86, 1.11	< 0.001	98.5
Heart disease											
No. of cases (*n* = 3126)	2507	520		84		51		135			
HR1 (model 1[b])	1.00	0.80	0.66, 0.96	0.88	0.71, 1.10	1.47	1.11, 1.95	0.92	0.79, 1.08	< 0.001	96.7
HR2 (model 2[c])	1.00	0.86	0.70, 1.05	0.91	0.71, 1.16	1.62	1.19, 2.22	0.97	0.81, 1.17	< 0.001	95.9
Stratified by smoking status											
No. of cases never	1982	361		52		30		82			
HR3 (model 1) never	1.00	0.80	0.66, 0.97)	0.99	0.75, 1.31	1.38	0.90, 2.11	1.03	0.81, 1.31	< 0.001	95.5
Stratified by smoking status											
No. of cases (*n* = 2900)	2267	527		66		40		106			
HR1 (model 1[b])	1.00	0.83	0.73, 0.95	0.71	0.50, 1.00	1.24	0.80, 1.91	0.79	0.61, 1.01	< 0.001	96.5
HR2 (model 2[c])	1.00	0.88	0.77, 1.00	0.77	0.54, 1.08	1.39	0.90, 2.14	0.83	0.62, 1.10	< 0.001	94.9
Stratified by smoking status											
No. of cases never	1793	364		42		18		60			
HR3 (model 1) never	1.00	0.82	0.70, 0.96	0.89	0.65, 1.22	1.34	0.78, 2.32	0.82	0.57, 1.17	< 0.001	93.9
Stratified by smoking status											
No. of cases (*n* = 1441)	1174	235		26		6		32			
HR1 (model 1[b])	1.00	0.80	0.69, 0.93	0.74	0.50, 1.10	0.64	0.29, 1.44	0.75	0.60, 0.95	< 0.001	92.8
HR2 (model 2[c])	1.00	0.80	0.68, 0.93	0.77	0.50, 1.17	0.75	0.33, 1.68	0.74	0.58, 0.95	< 0.001	91.4
Stratified by smoking status											
No. of cases never	941	169		16		3		19			
HR3 (model 2) never	1.00	0.87	0.72, 1.06	0.85	0.47, 1.54	0.78	0.25, 2.44	0.63	0.40, 1.00	< 0.001	90.3

(*continued on next page*)

Table 3 (*continued*)

	Coffee consumption										
	< 1 cup/day	1-2 cups/day		3-4 cups/day		≥5 cups/day		≥3 cups/day		Heterogeneity[d]	
	HR[a]	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	*P* for trend	%
Injuries and accidents											
No. of cases (n = 1259)	858		324		55		22		77		
HR1 (model 1[b])	1.00	1.01	0.87, 1.17	0.84	0.63, 1.11	1.24	0.80, 1.91	0.81	0.68, 0.97	< 0.001	96.0
HR2 (model 2[c])	1.00	1.02	0.84, 1.24	0.82	0.60, 1.12	1.37	0.87, 2.15	0.82	0.59, 1.15	< 0.001	95.0
Stratified by smoking status											
No. of cases never	713		253		36		11		47		
HR3 (model 1) never	1.00	0.98	0.84, 1.14	0.81	0.57, 1.15	1.17	0.62, 2.21	0.84	0.61, 1.15	< 0.001	95.4

Abbreviations: CI, confidence interval; HR, hazard ratio.

Missing: All mortality current smoker data MIYAGI, OHSAKI, 3-pref MIYAGI, 3-pref OSAKA; injury and accident data 3-pref MIYAGI, AICHI and OSAKA.

[a] Cox proportional hazards models were used with random effects.

[b] Model 1: Adjusted for age (years, continuous), area (JPHC and JACC only), smoking status (never, former, current), alcohol intake (none (never/former), < 1 times/week, regular (g/d) [< 23, ≥23]), BMI (< 18.5, 18.5 to < 25, 25 to < 30, ≥30 (< 14, ≥40 were treated as missing), history of diabetes (yes, no) and history of hypertension (yes, no), and green tea (cups/day).

[c] Model 2: Model 2 excluding incident cancer cases within 5 years.

[d] Heterogeneity across cohorts.

coffee consumption up to five cups per day reduced the risk of all-cause mortality. The magnitude of risk reduction (15–16%) associated with coffee consumption was comparable to two recent large cohort studies conducted in Western populations (Loftfield et al., 2018; Park et al., 2017). Our study corroborated the findings from previous Japanese cohort studies and added further epidemiologic evidence supporting the role of moderate coffee consumption (3–4 cups per day) in conveying health benefits in different ethnic populations.

We examined the association between coffee consumption and five major causes of death, and found that low doses (1–2 cups/day) of coffee were protective particularly for women in relation to heart and cerebrovascular disease. Regardless of dosage, coffee appeared to be protective against cerebrovascular disease in men. A 2014 meta-analysis observed a non-linear association between coffee intake with cardiovascular disease risk, with the lowest risk at 3 to 5 cups/day (Ding et al., 2014). A few mechanisms have been proposed to explain the inverse association between habitual coffee consumption and risk of cardiovascular diseases. Chlorogenic acid is a major phenolic compound in coffee, and has been shown to diminish the rate of glucose absorption (Johnston et al., 2003; van Dam and Hu, 2005) and lowers blood pressure (Yamaguchi et al., 2008). Chlorogenic acid may also reduce the risk of death from inflammatory diseases (Andersen et al., 2006). Another proposed mechanism underlying the protective role of coffee is related to caffeine, which is known to promote endothelial repair and improve pulmonary function (Spyridopoulos et al., 2008; Ale-Agha et al., 2018). A recent animal study demonstrated a new mode of action for caffeine; caffeine may protect and repair heart muscle through the action of mitochondrial p27, known as an inhibitor of the cell cycle (Ale-Agha et al., 2018). In addition, pyridinium compounds, formed upon trigonelline pyrolysis and coffee roasting, may be responsible for the beneficial effects of coffee drinking because of their antithrombotic properties (Kalaska et al., 2014).

Drinking a large amount of coffee, over 5 cups per day, increased the risk of heart disease by 47% among Japanese women in this pooled analysis. This could be due to other lifestyle habits such as high alcohol and tobacco consumption or increased blood pressure that may increase the risk of heart disease. The evidence is conflicting with regards to high intake of coffee and heart disease mortality. Two meta-analyses did not find an association between heavy coffee consumption and cardiovascular disease (Grosso et al., 2016; Ding et al., 2014). However, results were not reported separately by sex. Two individual studies found that drinking 4 or more cups (Klatsky et al., 1993) or 5 cups of coffee per day (Klag et al., 1994) increased risk for acute myocardial infarction and coronary heart disease (among men), respectively. In contrast to our study, Freedman et al. found drinking 6 or more cups of coffee to be inversely associated with heart disease in American women, while the 2–3 cups/day finding among men was similar to our results (Freedman et al., 2012). A Dutch study identified a positive association between coffee consumption and ischemic heart disease mortality in men, and an inverse relationship in women. Coffee consumption under 6 cups/day was associated with a lower risk of mortality from cardiovascular disease and stroke and under 3 cups per day for coronary heart disease, with the greatest risk reduction in the 3 cup category in a large meta-analysis (Grosso et al., 2016).

For mortality due to injuries and accidents, only daily coffee consumption of 3–4 cups/day was protective among men. The Nurses' Health Study and Kaiser Permanente Multiphasic Health Checkup cohorts reported similar results (Freedman et al., 2012; Klatsky et al., 1993; Kawachi et al., 1996). The mechanism is still unclear (Freedman et al., 2012). Freedman et al. suggested that the protective effect may reflect chance or residual confounding (Freedman et al., 2012).

Coffee consumption was not associated with overall cancer mortality, which is consistent with findings from two meta-analyses of cohort studies (Malerba et al., 2013; Yu et al., 2011). Previous epidemiological studies found inverse associations between coffee and risk of some site-specific cancers including: liver cancer (Inoue et al., 2009; Kurozawa et al., 2005; Larsson and Wolk, 2007), colon cancer in women (Je and Giovannucci, 2014; Kashino et al., 2018) and endometrial cancer (Shimazu et al., 2008). No association was reported with gastric cancer (Botelho et al., 2006), breast cancer (Harris et al., 2012), or thyroid cancer (Michikawa et al., 2011). An umbrella review of meta-analyses on coffee consumption and multiple health outcomes found colorectal (Galeone et al., 2010) and liver cancer (Bravi et al., 2017) to be among the 10 most beneficial, while lung (Galarraga and Boffetta, 2016) and urinary tract (Zeegers et al., 2001) cancer were among the 10 most harmful according to any versus no coffee consumption (Poole et al., 2017). For the purpose of this pooled analysis, we grouped cancer as one outcome. However, this null association may be masked with varying associations between coffee consumption and risk of site-specific cancer incidence and mortality. The report from the JPHC Study included a sensitivity analysis omitting deaths from liver and pancreatic cancer; however, the same null association remained (Saito et al., 2015).

After stratifying by smoking status, results remained similar among male current smokers and female never-smokers. Interestingly, consuming ≥3 cups of coffee per day was associated with increased risk of

death from respiratory disease among male never-smokers, whereas decreased risk was noted among male current smokers. The association was attenuated in the ≥5 cups/day group possibly due to the small number of deaths. There's a possibility of residual confounding by smoking, as the results were consistent even among never-smokers.

The primary strength of this study is the large sample size and the prospective nature of the individual Japanese cohorts, making the results of this pooled applicable to the general Japanese population. Despite several strengths, this analysis contains some limitations. Firstly, misclassification could have occurred as coffee consumption was measured at the time of the baseline study and habits may change over the course of time. Secondly, the analysis does not reflect the coffee content or preparation in more detail beyond the quantity consumed, e.g. drip coffee or addition of milk and sugar. Thirdly, we did not have information on the chemical make-up of the beverage, e.g. percent of chlorogenic acid, which may independently affect the risk of mortality (Saito et al., 2015). Fourthly, residual confounding or other confounders such as physical activity, education, menopausal status, total energy intake, red meat and fruit and vegetable consumption (Gunter et al., 2017) may influence the risk estimates. We were unable to adjust for physical activity as the questions in each cohort are different and only leisure time would have been available. Additionally, in the Japanese context even though it is acknowledged that there may be some effect between physical activity and coffee consumption it is not considered an established risk factor. For socio-economic status, at the time of the baseline study this topic was very sensitive and therefore there is no information on income or comparable education information across the cohorts. Fifthly, our analyses exhibited considerable heterogeneity (I^2 > 80%). Possible sources of heterogeneity include the type of coffee consumed, ascertainment of the exposure of interest or varying follow-up duration in the individual studies (Poole et al., 2017).

In this pooled analysis combining eight population-based cohort studies in Japan, we observed a protective effect of coffee consumption up to 5 cups/day for all-cause mortality, especially consumption of 1–2 cups/day was associated with decreased risk for cerebrovascular, respiratory disease and heart disease among women. The J-shaped curves observed in our study must be interpreted with caution as there were fewer cases in the high dose categories, low statistical power may have led to a lack of effect. Our analysis suggests coffee consumption under 5 cups/day may exhibit health benefits with regards to all-cause and cause-specific mortality.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2019.04.002.

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