Association of caffeine, green tea, and coffee consumption with mortality and disability among older adults

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Short title: Caffeine consumption and health outcomes

List of abbreviations: FFQ, food frequency questionnaire; DR, dietary record; HR, hazard ratio; CI, confidence interval

Abstract

Several epidemiological studies have shown that consumption of coffee and green tea is inversely associated with risks of death and disability; however, the relationship between caffeine consumption and these outcomes remains unclear. We examined these associations in Japanese older adults. This was a prospective study of 7,708 adults (aged ≥65 years) recruited from the Kyoto–Kameoka study. Dietary intake was estimated using a validated food frequency questionnaire. Caffeine consumption was classified into four categories. Disability and mortality data were collected between 15 February 2012 and 30 November 2016. Hazard ratios (HRs) and 95% confidence intervals (CIs) of outcomes were calculated using multivariable Cox proportional hazard models. During the median 4.75-year follow-up period, a total of 593 deaths and 1,379 disability incidents were recorded. After adjusting for confounders, caffeine consumption was inversely associated with the incidence of disability (<100 mg/day: reference; 100–149 mg/day: HR, 0.91 [95% CI, 0.80–1.04]; 150–199 mg/day: HR, 0.84 [95% CI, 0.72–0.99]; ≥200 mg/day: HR, 0.75 [95% CI, 0.63–0.89], p for trend = 0.001) but not all-cause mortality. High coffee consumption was inversely associated with mortality (≥3 cups/day: HR, 0.62 [95% CI, 0.43–0.88]) and disability (≥3 cups/day: HR, 0.81 [95% CI, 0.65–0.99]) compared with non-consumption. However, green tea consumption was not associated with mortality or disability. Caffeine and coffee consumption was inversely associated with disability and/or mortality. Further research is needed to clarify whether high caffeine intake is safe and effective for older adults.

Keywords: caffeine; food frequency questionnaire; prospective cohort study; long-term care insurance; dose-response relationship

INTRODUCTION

The populations of several developed countries are aging at unprecedented rates. The aging of the general population is directly linked to increased age-related disease burden and healthcare utilization[1]. Maintaining the independence of healthy older people is important for reducing these economic burdens.

Coffee and tea are consumed worldwide, with green tea being especially popular in Asia. The consumption of these beverages has been reported to be inversely associated with the risk of death[2] and incidences of disease and disability[3]. Although these beverages contain substances that have beneficial effects on health, such as polyphenols, they also contain caffeine[4], for which an upper limit of intake (400 mg/day) has been established[5, 6]. Excessive caffeine consumption can lead to increased sympathetic activity and circulating catecholamine concentrations through stimulation of the central nervous system[7], which may result in significant cardiovascular stress[8] and sleep disorders[9]. Therefore, evaluating the association between caffeine intake and health outcomes is necessary for determining the safety of habitual coffee and tea consumption.

While several epidemiological studies have indicated an inverse association between caffeine intake and the risk of mortality in adults[10-13], there are fewer studies compared to those on coffee and green tea consumption and health outcomes[3, 14]. Moreover, previous studies have focused on the relationship between quartiles of caffeine intake and the risk of death but not on the dose–response relationship between mortality risk and caffeine consumption. To our knowledge, no study has examined the relationship between caffeine consumption and the risks of mortality and disability in older adults.

In this cohort study, we aimed to evaluate the associations between caffeine, green tea, and coffee consumption and mortality and disability among older adults. Considering previous reports[10-13], we hypothesised that moderate caffeine, coffee, and green tea consumption is inversely associated with the risks of mortality and disability in older adults.

MATERIAL AND METHODS

Study population

This prospective cohort study examined the data of older adults aged ≥65 years who reside in Kameoka City, Kyoto Prefecture, Japan[15-21]. Of the individuals selected from the residents of Kameoka City aged ≥65 years (n = 19,424), those who required long-term care (n = 1170) and those who died between 1 July 2011 and 28 July 2011 (n = 23) were excluded (Figure 1). The remaining 18,231 participants completed the baseline survey on 29 July 2011. Of the residents whom the survey questionnaire was sent to, 13,294 responded (response rate: 72.9%). On 13 February 2012, we excluded the respondents who died or required long-term care. The remaining 11,985 respondents underwent an additional survey on 14 February 2012, which included completing a food frequency questionnaire (FFQ) that assesses dietary intake. Of the 11,985 respondents, 8,370 returned the questionnaire. Among them, 8,319 (response rate, 69.4%) provided valid responses, were individually identifiable from the questionnaire responses, and had sex information consistent with that obtained from the first and second surveys. Of those who participated in the additional survey (n=8,319), we excluded the respondents whose green tea (n=360) and coffee (n=167) consumption data were missing, those with a disability at the start of the follow-up (n=77), and those with no data on the date they moved out of Kameoka city (n=7). Thus, 7,708 participants were included in this study.

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Boards of the following institutions: National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN-76-2); Kyoto University of Advanced Science (No. 20-1); and Kyoto Prefectural University of Medicine (RBMR-E-363). Informed consent was obtained from all participants upon receiving their responses to the mail-in survey.

Dietary assessment

Dietary intake was evaluated using a self-administered FFQ that consisted of 47 items on food and beverage intake[22]. We previously validated the FFQ using dietary records (DRs)[18, 23] and doubly labelled water method[17]. The participants responded to questions regarding foods and beverage intake, including the amount of green tea and coffee consumed in the past year. The FFQ used in this study did not include questions about the brewing method of coffee or green tea. This FFQ consisted of the following eight response categories: never or seldom, 1–3 times per month, 1–2 times per week, 3–4 times per week, 5–6 times per week, once a day, twice a day, and three or more times a day. The following weights for beverage consumption frequencies were assigned to the abovementioned response categories: 0, 0.1, 0.2, 0.5, 0.8, 1.0, 2.0, and 3.0, respectively. Portion size was determined according to sex using a fixed value calculated from a one-day weighted DR (green tea: 220 g for men, 200 g for women, coffee: 100 g for both sexes)[22]. Green tea (r = 0.56 in both sex) and coffee consumption (r = 0.51 in men and 0.52 in women) estimated from this FFQ showed a moderate correlation with energy-adjusted green tea and coffee consumption assessed from the non-consecutive 3-day weighed DRs at 3-month intervals over four seasons in Japanese adults[23]. Furthermore, the mean intake of green tea and coffee estimated from the FFQ and DR did not differ significantly in both men (green tea: FFQ, 278 g/day; DR, 246 g/day and coffee: FFQ, 142 g/day; DR, 143 g/day) and women (green tea: FFQ, 306 g/day; DR; 289 g/day and coffee: FFQ, 155 g/day; DR, 128 g/day)[23]. The caffeine content of coffee and green tea was set at 60 mg and 20 mg per 100 g, respectively, based on the data in the Standard Tables of Food Composition in Japan[24]. Dietary intake, including caffeine consumption, was calculated from the intake frequency and portion size of each food and beverage using a program based on the Standard Tables of Food Composition in Japan[24].

Other covariates

All covariate data were obtained from a baseline questionnaire survey[20]. Body mass index was calculated by dividing the self-reported body weight by the height squared (kg/m^2). Data on the following covariates were also collected: smoking status ("Do you smoke?": almost daily; sometimes; used to, but quit; never), drinking status ("Do you drink alcohol?": almost daily, sometimes, almost never, never), sleep duration (minutes), living status ("What is your family structure?": living alone, living with family, other), education attainment (years), socioeconomic status ("Financially, how does your life feel currently?": hard, somewhat hard, somewhat easy, easy), oral status ("Do you use dentures?": yes, no), taking medication (number), and chronic disease ("Do you have a disease [presence of hypertension, stroke, heart disease, diabetes, hyperlipidaemia, gastrointestinal disease, respiratory disease, urological diseases, and cancer]?": yes, no). Comorbidity scores were calculated from the data obtained on the nine comorbidity statuses. The summed value yielded a total score ranging from 0 (no comorbidity) to 9 (poor status). The previous week's physical activity and sitting time per day were evaluated using the International Physical Activity Questionnaire-Short Form. Frailty was defined as a score ≥7 out of 25 items on the validated self-administered Kihon Checklist[25].

Mortality and disability status

The survival status of the participants during the follow-up period was assessed using data from the Basic Resident Register maintained by the Kameoka City Hall, whereas disability was determined using the Japanese Long-term Care Insurance Program[19, 26]. In the Japanese Long-Term Care Insurance Program, when an individual or their family perceived a need for care, an application for long-term care certification was submitted to the local municipal office. Following the application, a certified investigator—either a municipal employee or a contracted professional—visited the applicant's home to conduct a standardized assessment

comprising 74 items to evaluate the individual's physical and mental functions. Subsequently, the Long-Term Care Certification Committee, composed of physicians and other health and welfare professionals, reviewed all relevant information and determined the applicant's disability level. Because information on the disability status of residents is managed by municipalities, outcome data were provided by officials of the Kameoka City Hall and collected between February 15, 2012, and November 30, 2016. Participants whose records were administratively moved or removed from the municipality were censored.

Statistical analysis

Several previous studies have reported a 14% to 23% difference in the hazard ratios (HRs) for mortality when comparing the second and the first quartiles (or categories) of caffeine intake[10-12]. Based on this information, we used the "power cox" command in STATA to estimate the required sample size. A sample size of 460 to 1,381 would provide 80% power (1 − β error) at a 5% significance level to detect such differences. Therefore, the sample available for this study was deemed sufficiently large.

We classified the participants into the following caffeine intake categories according to the distribution of the exposure variables: <100 mg/day (n=2662), 100–149 mg/day (n=2161), 150–199 mg/day (n=1411), and ≥200 mg/day (n=1474). Coffee and green tea consumption was classified into the following four groups based on information from a previous study[21]: none, <1 cup/day, 1–2 cups/day, and ≥3 cups/day. The descriptive statistics for continuous and categorical variables were presented as means with standard deviation and frequencies with proportions, respectively. In cases of missing data, missing indicators were created for all the covariates.

We calculated each participant's person-years of follow-up from the date the additional questionnaire was returned to the date of death or disability, relocation from the study area, or end of follow-up, whichever occurred first. The all-cause mortality and disability rates for

each caffeine, green tea, and coffee consumption group are shown as the number of events per 1000 person-years. The multivariable Cox proportional hazards model included baseline covariates that were adjusted for the confounders associated with caffeine, green tea, and coffee consumption and mortality or disability. The model assumptions were confirmed using the Schoenfeld residual test (p=0.619). The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs), estimated using the lowest caffeine, green tea, and coffee consumption group as a reference. To evaluate the dose–response relationship between caffeine consumption and outcomes, we performed a multivariable-adjusted restricted cubic spline analysis with three knots (10^{th}, 50^{th}, and 90^{th} percentiles) based on the distribution of caffeine consumption. The results are presented as HRs (95% CIs), with the HRs calculated using 0 mg/day as the reference value. The linear trend *p* value was estimated by considering caffeine, green tea, and coffee consumption as continuous variables. We did not adjust for multiple comparisons in this study. As noted in previous literature[27], adjustment for multiple testing is not always necessary or appropriate, particularly in confirmatory analyses where the hypotheses are specified a priori. Unlike exploratory analyses involving a large number of variables or hypotheses, given the hypothesis-driven nature of our analysis and the limited number of predefined comparisons, we determined that multiple comparison adjustment was not warranted.

Sensitivity analysis was conducted using the following three methods: 1) exclusion of events (mortality: 31 women and 50 men; disability: 8 women and 9 men) recorded in the initial 1 year of follow-up to minimize the possibility of reverse causation, 2) performance of a similar analysis using a dataset wherein missing data for all covariates were imputed with multiple imputations, and 3) running a multivariable sub-distribution hazard model proposed by Fine and Gray to eliminate the problem of a cause-specific hazard model in which a 'competing event is censored'. In this analysis, disability was the event of interest, and mortality was a competing event. The multiple imputation analysis involved the evaluation of

pooled analysed results from 20 datasets created with random numbers. The multiple imputation method was employed to impute the missing of all covariates using the 'mi estimate' command in STATA. Missing values were presumed to be random.

The covariates used for the multivariable analysis included the potential confounders reported in previous studies[10-13, 16]. Model 1 included age (continuous), sex (female/male), and population density (≥1000 or <1000 people/km^2). Model 2 was adjusted for the variables in Model 1 plus body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2, or missing), alcohol consumption (never drank, past drinker, current drinker, or missing), smoking status (never smoked, past smoker, current smoker, or missing), family structure (living alone, living with others, or missing), education level (≤9, 10–12, ≥13 years, or missing), economic status (high, low, or missing), energy intake (continuous), physical activity (<150, 150–299, ≥300 min/week, or missing), sleep duration (<360, 360 to <420, 420 to <480, ≥480 min/day, or missing), sitting time (<5, 5 to <7, 7 to <9, ≥9 h/day, or missing), use of dentures (yes, no, or missing), medication use (none, 1, 2, 3, 4, ≥5, or missing), number of chronic diseases (continuous), and frailty status (yes or no).

A two-tailed probability of less than 5% was considered statistically significant. All statistical analyses were conducted using STATA MP (version 15.0; StataCorp LP, College Station, TX, USA).

RESULTS

Table 1 shows the baseline characteristics of the participants according to the caffeine consumption groups. The mean (standard deviation) caffeine consumption level of the participants was 129 (25) mg/day. The groups with high caffeine consumption levels consisted of younger participants; more women; and more participants with high educational attainment, who engaged in high levels of physical activity, and who were not on medications than the group with caffeine consumption level of <100 mg/day.

The associations between caffeine consumption, mortality, and disability are shown in Figures 2 and 3. The median follow-up period in this study was 4.75 years (interquartile range, 4.75–4.75 years). A total of 593 individuals (7.7%) died during the follow-up period (35,067 person-years), whereas 1,379 (17.9%) incidences of disabilities occurred during the follow-up period (32,588 person-years). After adjusting for confounders such as medical history and lifestyle, caffeine consumption was inversely associated with the incidence of disability (<100 mg/day: reference; 100–149 mg/day: HR, 0.91 [95% CI, 0.80–1.04]; 150–199 mg/day: HR, 0.84 [95% CI, 0.72–0.99]; ≥200 mg/day: HR, 0.75 [95% CI, 0.63–0.89], p for trend = 0.001) but not all-cause mortality. These association were similar to the results observed in the spline model (Figure 3). In addition, similar results were obtained in the sensitivity analyses (Supplementary Tables 1–3).

Table 2 shows the associations between green tea and coffee consumption and mortality and disability among older adults. High coffee consumption was inversely associated with mortality (≥3 cups/day: HR, 0.62 [95% CI, 0.43–0.88]) and disability (≥3 cups/day: HR, 0.81 [95% CI, 0.65–0.99]) compared with non-consumption. However, green tea consumption was not associated with mortality and disability.

DISCUSSION

The results of this study revealed a log linear inverse relationship between caffeine consumption and disability but not mortality and that coffee consumption, but not green tea consumption, was inversely associated with mortality and disability. To the best of our knowledge, this is the first study to evaluate the associations of caffeine, green tea, and coffee consumption with both incident mortality and disability.

The average caffeine consumption of our study sample was 129 mg/day. In a previous study of healthy Japanese adults aged 30–69 years, the average mean caffeine consumption estimated from the 16-day DRs of the participants was approximately 260 mg/day[28]. In

addition, previous studies have shown that middle-aged and older Japanese adults consume approximately 200 mg of caffeine per day[29], whereas older Americans with hypertension consume 146 mg of caffeine per day[10]. The estimated caffeine intake in our study was lower than that estimated in other studies, possibly because we calculated caffeine consumption using only two beverages (green tea and coffee) and because of differences in the methods used to estimate beverage intake, including portion size and consumption frequency. However, the most common categories of caffeine consumption among American adults are reported to be >0 to ≤100[11] and 10-99 mg/day[12], consistent with our findings. Therefore, although we could assess the relationship between health outcomes and the presence or absence of caffeine consumption in the present study, caffeine consumption should be estimated in future studies using more accurate dietary assessment methods to determine the dose–response relationship (especially at high doses) between caffeine intake and health outcomes.

Caffeine and coffee consumption, but not green tea consumption, was found to be inversely associated with mortality and disability. In several previous studies, caffeine[10-13] and coffee[13, 14] consumption has been reported to be inversely associated with the risk of mortality, similar to our results. However, in some studies, green tea consumption was found to be inversely associated with mortality[13] and the risks of disability[30] and diabetes[29]. In many previous studies, green tea consumption was estimated using questionnaires such as the FFQ, and mortality or disability data were obtained from public sources such as city halls[12, 30]. Therefore, no significant difference was observed between the methods used for the assessments of exposure factors and outcomes in the present study and in previous studies. In further studies, important factors, including population characteristics, that mediate the relationship between green tea consumption and health outcomes need to be clarified.

Consumption of up to 400 mg of caffeine per day is considered safe, and moderate coffee consumption can be included as part of a healthy lifestyle for most individuals[5, 6]. However,

a U-shaped relationship has been found between caffeine intake and the prevalence of cardiovascular disease[31]. Given that Japan's dietary guidelines do not include an upper limit for caffeine consumption and a description of its health benefits, our findings may provide valuable information for determining the optimal levels of caffeine consumption.

The reasons underlying the inverse association between coffee consumption and mortality and/or disability observed were unclear. However, the results can be attributed to two plausible reasons: First, coffee consumption is positively associated with skeletal muscle mass[32, 33] and grip strength (positive trend)[33] in Japanese people. Maintenance of skeletal muscle mass and grip strength has been shown to be inversely associated with mortality and disability in older adults[34]. However, the association between green tea consumption and skeletal muscle mass and grip strength has not been reported to date. The differences in the effects of these beverages support our results, which showed no association between green tea consumption and death or disability. Given that the beneficial effect of coffee consumption on skeletal muscle mass may not be related to its anti-inflammatory property as a mediator[33] and the antioxidant chlorogenic acid is only absorbed to approximately 33% in humans[35], other substances such as caffeine, may be involved in the health benefits of coffee consumption. Second, moderate caffeine consumption has multiple health benefits. Caffeine consumption has been reported to be inversely associated with the risk of depression[36]. In addition, consumption of coffee containing 4 mg of caffeine per body weight has been found to increase energy expenditure and fat oxidation compared with consumption of decaffeinated coffee[37]. In our previous cohort study, depressive status[15] and body mass index[16] were associated with the risk of mortality; hence, the multiple beneficial effects of caffeine consumption may be related to improved prognosis in older people[4, 6]. However, interventional and basic research is needed to identify the causal relationship between caffeine and coffee consumption and health outcomes and clarify the underlying mechanisms.

The primary strength of this study was that we evaluated the relationships between caffeine, green tea, and coffee consumption and mortality and disability in a large cohort of older adults from Kameoka City. However, this study had some methodological limitations. First, the dietary intake estimated using the self-administered FFQ may have been affected by the self-reporting errors related to participant characteristics[17], hindering accurate evaluation of dietary food and beverage consumption. Although a previous study demonstrated that coffee and tea consumption account for about 96% of the caffeine intake of Japanese older adults[28], caffeine consumption levels may have been underestimated in the present study if the older adults actually consumed caffeine from other types of foods and beverages apart from green tea and coffee. In addition, the caffeine content of beverages such as coffee and tea can differ according to the fermentation methods of tea leaves and preparation (brewing) methods, such as the length of infusion, cup size, and temperature[38]. Decaffeinated coffee is not commonly consumed in Japan[28], but we cannot exclude the possibility that some participants consumed decaffeinated coffee. Therefore, the absolute value of caffeine consumption reported in this study should be interpreted with caution. Second, the participants included in this study may have been more health-conscious than the additional survey participants or the general population because only the residents who were alive at the time of the additional surveys could provide responses to the questionnaires. Third, the follow-up period was relatively short. This may partially explain why we did not observe an association between caffeine intake and mortality risk; future studies with longer follow-up periods are needed to re-evaluate these relationships. In addition, we were unable to examine the association between the exposure variables and cause-specific death because we could not obtain data on causes of death. Finally, although various confounders were adjusted in this study, residual confounders may have impacted the association between the exposure variables and outcomes. In addition, age-related changes in covariates, such as alcohol consumption, may have introduced systematic bias in studies examining associations with

health outcomes[39]. Therefore, future research should employ longitudinal data that capture time-varying exposures and covariates to more accurately assess their relationships with outcomes.

CONCLUSIONS

This study revealed a log linear inverse relationship between caffeine consumption and disability but not mortality. We observed that coffee consumption, but not green tea consumption, was inversely associated with mortality and disability. Therefore, a slight increase in caffeine consumption in a dose-dependent manner over a range of doses, from about 0 to 320 mg/day, is inversely associated with the risk of disability. However, further research is needed to determine whether a higher caffeine consumption than that evaluated in this study will be effective in reducing the incidence of disability in older adults without adverse events. The findings of this study may provide insights into the optimal caffeine and coffee consumption levels necessary for improving and maintaining the health of older adults.

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Declaration of Interests

The author(s) declare none.

Authorship contributions

DW conceptualised the study. TY, HN, YY, and MK managed the project. TY, YW, YY, and MK performed data acquisition or entry. DW performed the literature review. DW performed the data analyses. DW contributed towards creation of graphics. DW wrote the first draft of the manuscript. All authors contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Data availability

All data sharing and collaboration requests should be directed to the corresponding author (d-watanabe@nibn.go.jp), TY (t-yoshida@nibiohn.go.jp), and YY (yamaday@nibiohn.go.jp).

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Table 1. Baseline characteristics of the study participants according to group of caffeine consumption

	Total (*n* = 7708)		Groups of caffeine consumption (mg/day)							
			<100 (n = 2662)		100-149 (n = 2161)		150-199 (n = 1411)		≥200 (n = 1474)	
Age [years]*	73.3	(6.1)	73.6	(6.1)	73.6	(6.3)	73.3	(6.0)	72.3	(5.6)
Women [n (%)]†	4074	(52.9)	1207	(45.3)	1185	(54.8)	803	(56.9)	879	(59.6)
PD ≥1000 people/km^2 [n (%)]†	3538	(45.9)	1236	(46.4)	982	(45.4)	649	(46.0)	671	(45.5)
Body mass index [kg/m^2]*	22.7	(3.4)	22.8	(3.4)	22.6	(3.2)	22.5	(3.2)	22.7	(3.8)
Living alone [n (%)]†	852	(11.1)	266	(10.0)	252	(11.7)	168	(11.9)	166	(11.3)
HSES [n (%)]†	2549	(33.1)	836	(31.4)	707	(32.7)	495	(35.1)	511	(34.7)
Education ≥13 y [n (%)]†	1620	(21.0)	521	(19.6)	432	(20.0)	309	(21.9)	358	(24.3)
Current smoker [n (%)]†	811	(10.5)	287	(10.8)	184	(8.5)	166	(11.8)	174	(11.8)
Alcohol drinker [n (%)]†	4883	(63.3)	1736	(65.2)	1322	(61.2)	873	(61.9)	952	(64.6)
Physical activity [min/week]*	240	(448)	231	(449)	228	(417)	249	(468)	265	(472)
Sitting time [min/day]*	310	(216)	302	(216)	318	(219)	330	(227)	291	(199)
Sleep time [min/day]*	403	(81)	407	(86)	402	(78)	402	(83)	395	(77)
Denture use [n (%)]†	4509	(58.5)	1563	(58.7)	1255	(58.1)	841	(59.6)	850	(57.7)
No medication [n (%)]†	1631	(21.7)	496	(18.6)	435	(20.1)	304	(21.6)	396	(26.9)
Hypertension [n (%)]†	2912	(37.8)	1029	(38.7)	875	(40.5)	529	(37.5)	479	(32.5)
Stroke [n (%)]†	268	(3.5)	122	(4.6)	70	(3.2)	39	(2.8)	37	(2.5)
Heart disease [n (%)]†	923	(12.0)	365	(13.7)	262	(12.1)	157	(11.1)	139	(9.4)
Diabetes [n (%)]†	767	(10.0)	293	(11.0)	202	(9.4)	143	(10.1)	129	(8.8)
Hyperlipidaemia [n (%)]†	746	(9.7)	235	(8.8)	211	(9.8)	149	(10.6)	151	(10.2)
Digestive disease [n (%)]†	621	(8.1)	249	(9.4)	183	(8.5)	106	(7.5)	83	(5.6)

Respiratory disease [n (%)][†]	349	(4.5)	121	(4.6)	101	(4.7)	72	(5.1)	55	(3.7)
Urological diseases [n (%)][†]	451	(5.9)	177	(6.7)	143	(6.6)	71	(5.0)	60	(4.1)
Cancer [n (%)][†]	231	(3.0)	91	(3.4)	65	(3.0)	40	(2.8)	35	(2.4)
No. of chronic diseases[*,‡]	0.94	(0.96)	1.01	(1.01)	0.98	(0.97)	0.93	(0.93)	0.79	(0.88)
Frailty [n (%)][†]	2370	(30.8)	946	(35.5)	666	(30.8)	389	(27.6)	369	(25.0)
Energy intake [kcal/day][*]	1737	(475)	1714	(500)	1725	(467)	1756	(462)	1776	(452)
[kJ/day][*]	7267	(1987)	7173	(2092)	7218	(1954)	7345	(1933)	7432	(1891)
No green tea consumption [n (%)][†]	1042	(13.5)	764	(28.7)	182	(8.4)	96	(6.8)	0	(0.0)
No coffee consumption [n (%)][†]	922	(12.0)	570	(21.4)	352	(16.3)	0	(0.0)	0	(0.0)
Caffeine intake [mg/day][*]	129	(25)	41	(27)	124	(15)	177	(13)	252	(37)

HSES, high socioeconomic status; PD, population density

Number of missing values for the variables are as follows: body mass index, n = 28 (0.4%); family structure, n = 566 (7.3%); socioeconomic status, n = 344 (4.5%); educational attainment, n = 842 (10.9%); smoking status, n = 317 (4.1%); alcohol drinking, n = 278 (3.6%); physical activity, n = 197 (2.6%); sitting time, n = 811 (10.5%); sleep time, n = 359 (4.7%); denture use, n = 193 (2.5%); medications use, n = 574 (7.4%); and frailty status, n = 950 (12.3%). Body mass index was calculated as body weight (kg) divided by height squared (m^2).

[*] Continuous values are shown as mean (standard deviation).

[†] Categorical values are shown as number (percentage).

[‡] From the data obtained on the disease status (including the presence of hypertension, stroke, heart disease, diabetes, hyperlipidaemia, digestive disease, respiratory disease, urological diseases, and cancer), the comorbidity scores were summed to obtain a total score ranging from 0 (no comorbidity) to 9 (poor status).

Table 2. Hazard ratios for all-cause mortality and disability according to the green tea and coffee consumption frequency, calculated using multivariable Cox proportional hazards analysis

	Frequency of green tea and coffee consumption												*p* for trend
	None			<1 cup/day			1–2 cups/day			≥3 cups/day			
All-cause mortality													
Green tea, n	1042			2015			1947			2704			
No of deaths (PY)	86	(4717)		142	(9209)		144	(8861)		221	(12281)		
Rate/1000 PY (95% CI)	18.2	(14.8	to 22.5)	15.4	(13.1	to 18.2)	16.3	(13.8	to 19.1)	18.0	(15.8	to 20.5)	
Model 1*	1.00	(Ref)		0.94	(0.72	to 1.23)	0.90	(0.69	to 1.18)	0.97	(0.75	to 1.24)	0.884
Model 2†	1.00	(Ref)		0.99	(0.76	to 1.30)	1.06	(0.81	to 1.39)	1.10	(0.85	to 1.43)	0.326
Coffee, n	922			1980			3931			875			
No of deaths (PY)	121	(4074)		166	(8957)		262	(17980)		44	(4057)		
Rate/1000 PY (95% CI)	29.7	(24.9	to 35.5)	18.5	(15.9	to 21.6)	14.6	(12.9	to 16.4)	10.8	(8.1	to 14.6)	
Model 1*	1.00	(Ref)		0.69	(0.55	to 0.88)	0.65	(0.52	to 0.81)	0.58	(0.41	to 0.82)	<0.001
Model 2†	1.00	(Ref)		0.73	(0.58	to 0.93)	0.73	(0.59	to 0.91)	0.62	(0.43	to 0.88)	0.005
Disability													
Green tea, n	1042			2015			1947			2704			
No. of disability (PY)	189	(4359)		335	(8623)		358	(8227)		497	(11379)		
Rate/1000 PY (95% CI)	43.4	(37.6	to 50.0)	38.9	(34.9	to 43.2)	43.5	(39.2	to 48.3)	43.7	(40.0	to 47.7)	

Model 1*	1.00	(Ref)		0.97	(0.81	to	0.92	(0.77	to	0.84	(0.71	to	0.99)	0.014
Model 2†	1.00	(Ref)		1.01	(0.85	to	1.08	(0.90	to	0.96	(0.81	to	1.14)	0.567
Coffee, n	922			1980			3931			875				
No. of disability (PY)	255	(3592)		449	(8086)		564	(17042)		111	(3868)			
Rate/1000 PY (95% CI)	71.0	(62.8	to	80.3)	55.5	(50.6	to	60.9)	33.1	(30.5	to	35.9)	28.7	(23.8	to	34.6)	
Model 1*	1.00	(Ref)		0.98	(0.84	to	1.15)	0.67	(0.57	to	0.77)	0.75	(0.60	to	0.95)	<0.001
Model 2†	1.00	(Ref)		1.01	(0.87	to	1.19)	0.74	(0.63	to	0.86)	0.81	(0.65	to	0.99)	<0.001

CI, confidence interval; PY, person-years; Ref, reference.

* Model 1: Adjusted for age, sex, and population density. Results are shown as hazard ratios (95% CI).

† Model 2: In addition to the factors listed in Model 1, adjusted for body mass index, family structure, economic status, educational attainment, smoking status, alcohol consumption status, energy intake, physical activity, sitting time, sleep time, denture use, medication use, number of chronic diseases, and frailty status. Results are shown as hazard ratios (95% CI).

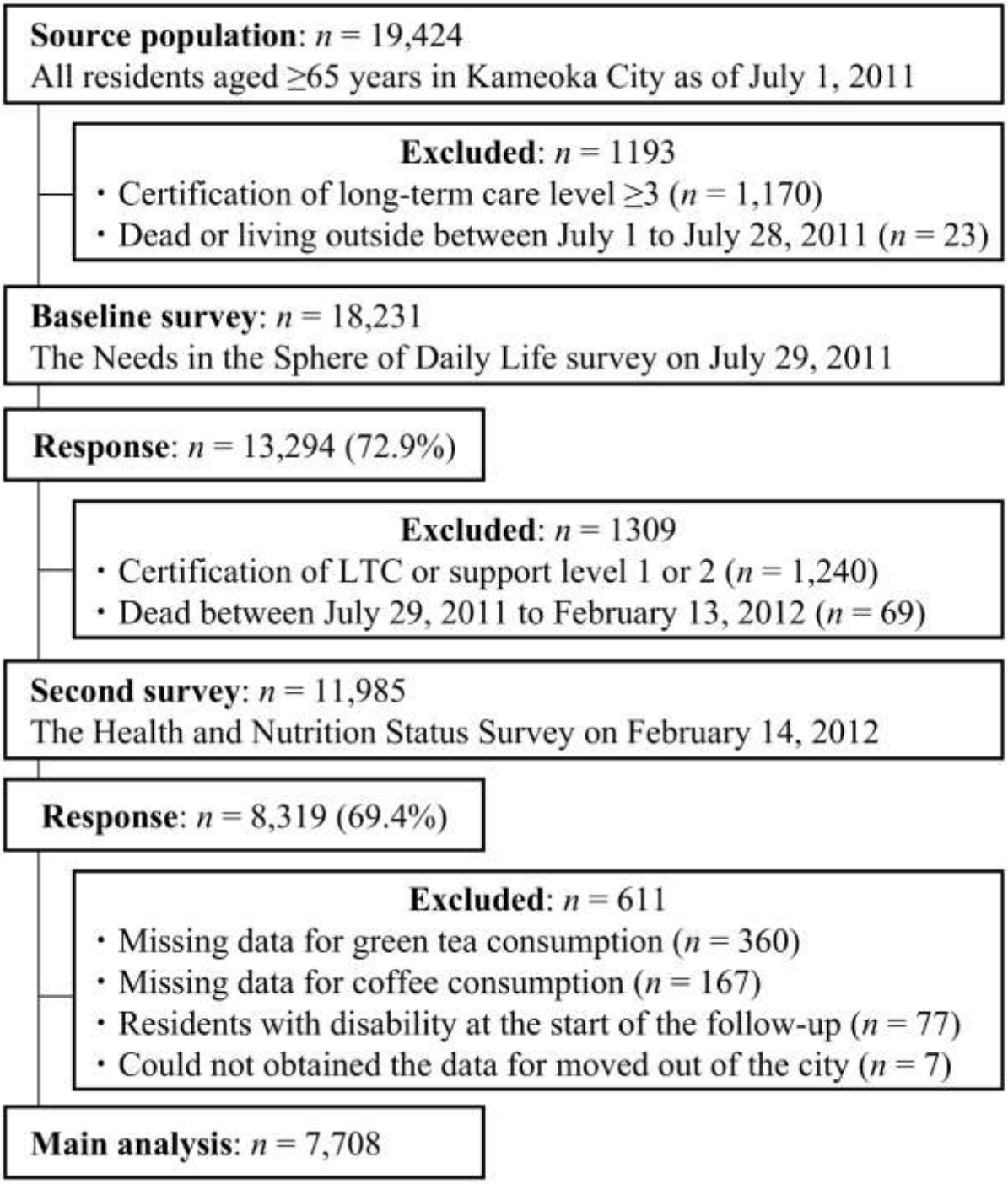

Figure 1 Participant flow diagram for the analysis of the relationship between caffeine, green tea, and coffee consumption and disability and mortality in the Kyoto–Kameoka study

LTC, long-term care

Caffeine groups (mean [mg/day])	*n*	PY	No of event	Rate/1000 PY (95% CI)	Hazard ratio (95% CI) Model 1	Model 2
All-cause mortality						
<100 (41)	2662	12031	232	19.3 (17.0 to 21.9)	1.00 (Ref)	1.00 (Ref)
100-149 (124)	2161	9799	176	18.0 (15.5 to 20.8)	0.94 (0.77 to 1.14)	1.01 (0.83 to 1.23)
150-199 (177)	1411	6430	109	17.0 (14.0 to 20.5)	0.95 (0.76 to 1.19)	1.02 (0.81 to 1.28)
≥200 (252)	1474	6807	76	11.2 (8.9 to 14.0)	0.72 (0.56 to 0.94)	0.81 (0.62 to 1.05)
Caffeine 100 mg/day increment					0.88 (0.77 to 0.98)	0.93 (0.82 to 1.03)
p for trend					0.018	0.178
Disability						
<100 (41)	2662	10992	551	50.1 (46.1 to 54.5)	1.00 (Ref)	1.00 (Ref)
100-149 (124)	2161	9074	421	46.4 (42.2 to 51.0)	0.85 (0.75 to 0.97)	0.91 (0.80 to 1.04)
150-199 (177)	1411	6005	225	37.5 (32.9 to 42.7)	0.76 (0.65 to 0.89)	0.84 (0.72 to 0.99)
≥200 (252)	1474	6517	182	27.9 (24.2 to 32.3)	0.66 (0.55 to 0.78)	0.75 (0.63 to 0.89)
Caffeine 100 mg/day increment					0.81 (0.74 to 0.88)	0.88 (0.81 to 0.95)
p for trend					< 0.001	0.001

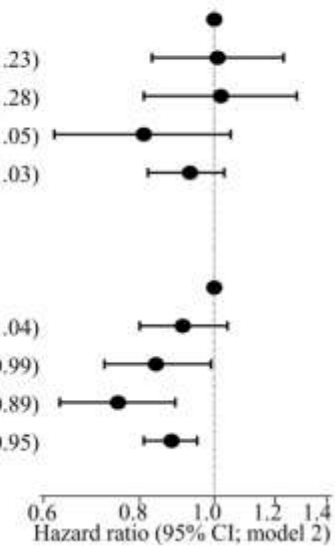

Figure 2 Forest plot of hazard ratios for mortality and disability according to the caffeine consumption, calculated using multivariable Cox proportional hazards analysis

Model 1 was adjusted for age, sex, and population density; Model 2 was additionally adjusted for body mass index, family structure, economic status, educational attainment, smoking status, alcohol consumption status, energy intake, physical activity, sitting time, sleep time, denture use, medication use, number of chronic diseases, and frailty status. The x-axis of the plot is on a log scale. CI, confidence interval; PY, person-years; Ref, reference

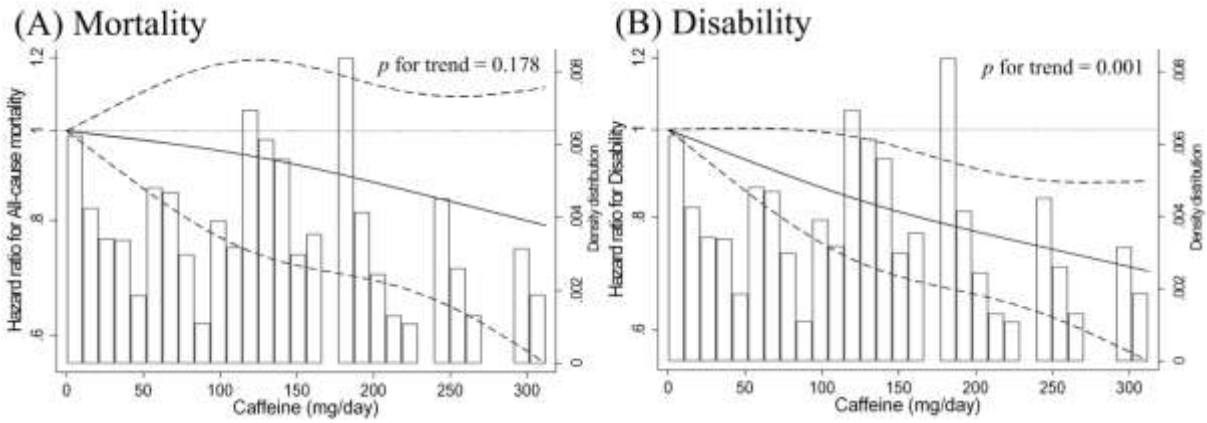

Figure 3 Multivariable adjusted restricted cubic spline model for caffeine consumption with mortality and disability among older adults

The histogram shows the distribution of caffeine consumption. The hazard ratio based on the 0 mg/day of caffeine consumption as reference was calculated. The adjustment factors are age, sex, population density, body mass index, family structure, economic status, educational attainment, smoking status, alcohol consumption status, energy intake, physical activity, sitting time, sleep time, denture use, medication use, number of chronic diseases, and frailty status. Solid lines represent hazard ratios, and dashed lines represent 95% confidence intervals.