

## Article

# Milk intake and stroke mortality in the Japan Collaborative Cohort Study - a Bayesian survival analysis

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**Abstract:** A single paragraph of about 200 words maximum. For research articles, abstracts should give a pertinent overview of the work. We strongly encourage authors to use the following style of structured abstracts, but without headings: 1) Background: Place the question addressed in a broad context and highlight the purpose of the study; 2) Methods: Describe briefly the main methods or treatments applied; 3) Results: Summarize the article's main findings; and 4) Conclusion: Indicate the main conclusions or interpretations. The abstract should be an objective representation of the article, it must not contain results which are not presented and substantiated in the main text and should not exaggerate the main conclusions.

**Keywords:** milk intake; mortality; stroke; Bayesian survival analysis; time-to-event data; JACC study

## 1. Introduction

Dairy food, especially milk has been recommended to reduce stroke risk by nearly 7% for each 200 g increment of daily consumption [1]. More intuitive interpretation for a decreasing risk would be possible if we were able to compute the exact probability for people who had milk intake may had lower hazard of dying from stroke compared with those who never drank milk at all. For general public/media reporting, concept of hazard in epidemiological studies could still sometimes be challenging to be understood or misinterpreted since hazard is formally defined as the probability of the occurrence of an event at a given time point [2]. Usually, authors of epidemiological papers would tend to use “risk” instead of “hazard” or interchangeably. However, it would still possibly be mixed up with “risk” that only contain pure meaning of “probability of an event” without redefining a point or a period of time in cross-sectional settings. For better understanding and interpretation of the findings from data that researchers endeavored to collect, statistical literature have provided plenty of choices that could help us better communicate with each other. Another approach of comparing the time-to-event survival probabilities between different groups would be to model the time before observing an event rather than the hazard which always required the assumption of a proportional hazard. Accelerated failure time models are among these convenient tools that would avoid frequently unmet assumption of proportional hazard and directly show how faster/slower that one individual in an exposure group might have an event compared to others among different exposure groups [3].

Our aim was to overcome these potential pitfalls, avoid misunderstanding, and provide a more straightforward answer to the main research question that whether someone answered he/she drank milk at the baseline of study had lower hazard of dying from stroke compared with his/her counterparts who said they never consumed milk. If the answer to the primary objective was yes, then the probabilities that individuals with different frequencies of milk intake may had lower hazard compared with those who never drank milk were calculated through a Markov Chain Monte Carlo (MCMC) simulation process. A Bayesian survival analysis method was applied on an existing database and through which, we also provided estimates about whether drinking milk could delay or slow down the speed towards a stroke event from happening after controlling for the other potential confounders.

## 2. Materials and Methods

### 2.1. The database

We used data from the Japan Collaborative Cohort (JACC) study, which was sponsored by the Ministry of Education, Sports, Science, and Technology of Japan. Sampling methods and details about the JACC study have been described extensively in the literature [4–6]. Participants of the JACC study completed self-administered questionnaires about their lifestyles, food intake (food frequency questionnaire, FFQ), and medical histories of cardiovascular disease or cancer. In the final follow-up of the JACC study, data from a total of 110585 individuals (46395 men and 64190 women) were successfully retained for the current analysis. We further excluded samples if they meet one of the following criteria: 1) with any disease history of stroke, cancer, myocardial infarction, ischemic heart disease, or other types heart disease ( $n = 6655$ , 2931 men and 3724 women); 2) did not answer the question regarding their milk consumption in the baseline FFQ survey ( $n = 9545$ , 3593 men and 5952 women). Finally, 94385 (39386 men and 54999 women) are left in the database. The study design and informed consent procedure were approved by the Ethics Review Committee of Nagoya University School of Medicine.

### 2.2. Exposure and the outcome of interest

Frequency of milk intake during the preceding year of the baseline was assessed by FFQ from “never”, “1-2 times/month”, “1-2 times/week”, “3-4 times/week”, and “Almost daily”. The exact amount of milk consumption was difficult to assess here. However, good reproducibility and validity were confirmed previously (Spearman rank correlation coefficient between milk intake frequency and weighed dietary record for 12 days was 0.65) [7].

The causes and date of death were obtained from death certificates and were systematically reviewed. The follow-up period was defined as from the time of the baseline survey was completed, which was between 1988-1990, until the end of 2009 (administrative censor), or the date when move-out of study area, or the date of death from stroke recorded, whichever occurred first. Other causes of death were treated as censored and assumed not informative. The causes of death were coded by the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), therefore stroke was defined as I60-I69. We further classified these deaths into hemorrhagic stroke (I60, I61 and I62) or cerebral infarction (I63) when subtypes of stroke in their death certificates were available.

### 2.3. Statistical approach

We calculated sex-specific means (standard deviation, sd) and proportion of selected baseline characteristics according to the frequency of milk intake. Overall difference across the milk intake groups were tested by either analysis of variance for continuous variables or  $\chi^2$  test for categorical variables.

Full parametric proportional hazard models under Bayesian framework with Weibull distribution were fitted using Just Another Gibbs Sampler (JAGS) program [8] version 4.3.0 in R version 4.0.1 [9]. JAGS program is similar to the OpenBUGS [10] project that uses a Gibbs sampling engine for MCMC simulation. In the current analysis, we specified non-informative prior distributions for each of the parameters in our models ( $\beta_n \sim N(0, 1000)$ , and  $\kappa_{\text{shape}} \sim \Gamma(0.001, 0.001)$ ). The Brooks-Gelman-Rubin diagnostic [11] was used to refine the approximate point of convergence, the point when the ratio of the chains is stable around 1 and the within and between chain variability start to reach stability was visually checked. The auto-correlation tool further identified if convergence has been achieved or if a high degree of auto-correlation exists in the sample. Then, the number of iterations discarded as ‘burn-in’ was chosen. All models had a posterior sample size of 100000 from four separated chains with a “burn-in” of 2500 iterations. Posterior means (sd) and 95% Credible Intervals (CrI) of the estimated hazard ratios (HRs) as well as acceleration factors (AFs) were presented for each category of milk intake frequency taking the “never” category as the reference. Posterior probabilities that the estimated hazard of dying from stroke for the milk intake for frequency that higher or equal to “1-2 times/month” is smaller compared with those who chose “never” to their milk intake frequency were calculated as  $P(\text{HR} < 1)$ .

The parametric forms of the models fitted in the Bayesian survival analyses included three models: 1) the crude model, 2) the age-centered adjusted model, 3) and a model further adjusted for potential confounders which includes: age (centered, continuous), smoking habit (never, current, former), alcohol intake (never or past, < 4 times/week, Daily), body mass index (< 18.5,  $\geq 18.5$  and < 25,  $\geq 25$  and < 30,  $\geq 30$  kg/m<sup>2</sup>), history of hypertension, diabetes, kidney/liver diseases (yes/no), exercise (more than 1 hour/week, yes/no), sleep duration (< 7,  $\geq 7$  and < 8,  $\geq 8$  and < 9,  $\geq 9$ , hours), coffee intake (never, < 3-4 times/week, almost daily), education level (attended school till age 18, yes/no)

### 3. Results

The total follow-up was 1555073 person-years (median = 19.3 years), during which 2675 death from stroke was confirmed (1352 men and 1323 women). Among these stroke mortality, 952 were hemorrhagic stroke (432 men and 520 women), and 957 were cerebral infarction (520 men and 437 women).

As listed in **Table 1**, compared with those who chose “never” as their milk intake frequency at baseline, milk drinkers were less likely to be a current smoker or a daily alcohol consumer in both men and women. Furthermore, people consumed milk more than 1-2 times/month were more likely to be a daily consumers of vegetable, fruit as well as coffee, and more likely to join exercise more than 1 hour/week among either sex.

Detailed results from the Bayesian survival models (crude, age-adjusted and multivariable adjusted) according to the frequency of milk intake separated by sex are listed in **Table 2** (men) and **Table 3** (women). Compared to those who never had milk, both men and women had lower hazard of dying from total stroke in crude models. Chances that the posterior HRs were estimated to be lower than 1 for those who had at least 1-2 times/month was higher than 86.5% in men and more than 94.6% in women. However, lower hazard was observed to remain after age or multivariable adjustment only in men. Specifically, the mean (sd; 95% CrI) of posterior multivariable-adjusted HRs for daily male consumers of milk was 0.80 (sd = 0.07; 95% CrI: 0.69, 0.93) with a probability of 99.0% to be smaller than the null value (=1). Daily female milk consumers had posterior HRs that was distributed with mean (sd) of 0.95 (sd = 0.12; 95% CrI: 0.80, 1.17) which had 78.0% of chance that their HRs could be lower than 1.

Posterior distributions of HRs for mortality from hemorrhagic stroke were found to contain the null value for either men or women among all fitted models. In contrast, men who had milk intake frequency higher than 1-2 times/week were found to be associated with averagely 26%-37% lower hazard of dying from cerebral infarction compared with men who never drank milk (Model 2 in **Table**

**Table 1.** Sex-specific baseline characteristics according to the frequency of milk intake (JACC study, 1988-2009).

	Never	Drinker	Milk drinkers				P value
			1-2 times/ Month	1-2 times/ Week	3-4 times/ Week	Almost Daily	
<b>Men (n = 39386)</b>							
number of subjects	8508	30878	3522	5928	5563	15865	
Age, year (mean (SD))	56.8 (9.9)	56.8 (10.2)	55.2 (10.1)	55.4 (10.1)	55.4 (9.9)	58.1 (10.1)	<0.001
Current smoker, %	58.7	49.8	57.4	55.9	51.1	45.4	<0.001
Daily alcohol drinker, %	51.9	47.8	50.9	48.4	48.6	46.5	<0.001
BMI, kg/m <sup>2</sup> (mean (SD))	22.6 (3.4)	22.7 (3.4)	22.8 (2.8)	22.8 (2.8)	22.9 (5.4)	22.6 (2.8)	<0.001
Exercise (> 1h/week), %	19.0	27.6	26.5	25.0	25.5	29.5	<0.001
Sleep duration, 8-9 hours, %	35.6	35.9	34.6	36.2	35.1	36.3	<0.001
Vegetable intake, daily, %	21.3	25.4	20.1	20.4	20.8	30.1	<0.001
Fruit intake, daily, %	14.8	22.4	15.4	16.3	17.3	28.1	<0.001
Green tea intake, daily, %	76.5	79.2	79.9	78.3	77.9	79.8	<0.001
Coffee intake, daily, %	43.8	50.7	50.5	48.0	47.5	52.9	<0.001
Educated over 18 years old, %	25.5	34.7	33.8	33.3	31.0	36.6	<0.001
History of diabetes, %	5.5	6.3	4.5	4.2	5.5	7.7	<0.001
History of hypertension, %	18.4	17.9	17.5	17.1	16.8	18.7	0.039
History of kidney diseases, %	3.0	3.4	3.8	3.0	3.0	3.5	<0.001
History of liver diseases, %	5.8	6.5	6.3	6.0	5.4	7.2	<0.001
<b>Women (n = 545999)</b>							
number of subjects	10407	44592	3640	7590	8108	25254	
Age, year (mean (SD))	58.0 (10.2)	56.9 (9.9)	56.5 (10.2)	55.6 (10.1)	55.6 (9.9)	57.9 (9.9)	<0.001
Current smoker, %	6.9	4.2	6.1	5.5	4.3	3.5	<0.001
Daily alcohol drinker, %	4.3	4.5	5.5	4.3	4.2	4.6	<0.001
BMI, kg/m2 (mean (SD))	23.0 (3.4)	22.9 (3.7)	23.0 (3.8)	23.1 (4.4)	23.1 (3.1)	22.8 (3.6)	<0.001
Exercise (> 1h/week), %	13.6	20.8	17.1	18.5	18.8	22.6	<0.001
Sleep duration, 8-9 hours, %	27.7	25.6	25.1	25.9	25.4	25.7	<0.001
Vegetable intake, daily, %	24.7	30.4	25.0	24.6	24.2	34.8	<0.001
Fruit intake, daily, %	25.0	35.7	26.6	29.2	29.2	41.1	<0.001
Green tea intake, daily, %	73.8	76.8	77.0	76.4	75.8	77.3	<0.001
Coffee intake, daily, %	39.6	48.2	46.2	46.4	44.4	50.2	<0.001
Educated over 18 years old, %	19.9	31.6	27.9	29.8	27.4	34.0	<0.001
History of diabetes, %	2.6	3.7	3.2	2.7	2.7	4.4	<0.001
History of hypertension, %	21.5	19.7	20.5	19.1	18.9	20.0	<0.001
History of kidney diseases, %	3.6	4.1	3.9	3.7	3.7	4.4	<0.001
History of liver diseases, %	3.5	4.6	4.9	3.9	3.9	5.0	<0.001

2). We were more than 95.7% sure that these posterior HRs could be lower than 1. No associations were observed between milk intake and hazard of cerebral infarction among women.

#### 4. Discussion

In the JACC study cohort, we observed that

#### 5. Conclusion

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**Author Contributions:** “X.X. and Y.Y. conceive and designed the experiments; X.X. performed the experiments; X.X. and Y.Y. analyzed the data; W.W. contributed reagents/materials/analysis tools; Y.Y. wrote the paper.”

**Conflicts of Interest:** The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, an in the decision to publish the results.

#### Abbreviations

The following abbreviations are used in this manuscript:

JACC	Japan Collaborative Cohort
FFQ	Food Frequency Questionnaire
MCMC	Markov Chain Monte Carlo
JAGS	Just Another Gibbs Samplers
AFT	accelerated failure time
HR	hazard ratio
AF	acceleration factor
sd	standard deviation
CrI	credible interval

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**Table 2.** Summary of posterior Acceleration Factors (AF) and Hazard Ratios (HR) of mortality from total stroke, stroke types according to the frequency of milk intake in men (JACC study, 1988–2009).

	Never	1-2 times/Month	1-2 times/Week	3-4 times/Week	Almost Daily
Person-year	135704	56551	97098	92153	252364
N	8508	3522	5928	5563	15865
Total Stroke	326	122	181	177	546
<b>Model 0</b>					
Mean AF (SD)	1	0.93 (0.07)	0.83 (0.05)	0.85 (0.05)	0.93 (0.04)
95% CrI	-	(0.81, 1.06)	(0.73, 0.94)	(0.74, 0.96)	(0.85, 1.02)
MeanHR (SD)	1	0.89 (0.09)	0.77 (0.07)	0.79 (0.07)	0.90 (0.06)
95% CrI	-	(0.73, 1.08)	(0.63, 0.91)	(0.66, 0.94)	(0.79, 1.03)
Pr(HR < 1)	-	86.50%	99.90%	99.70%	93.50%
<b>Model 1</b>					
Mean AF (SD)	1	0.99 (0.06)	0.90 (0.05)	0.91 (0.05)	0.85 (0.04)
95% CrI	-	(0.87, 1.11)	(0.81, 1.00)	(0.82, 1.01)	(0.78, 0.92)
MeanHR (SD)	1	0.98 (0.11)	0.84 (0.08)	0.86 (0.08)	0.76 (0.05)
95% CrI	-	(0.79, 1.19)	(0.70, 1.00)	(0.71, 1.02)	(0.66, 0.87)
Pr(HR < 1)	-	58.70%	97.30%	96.10%	100.00%
<b>Model 2</b>					
Mean AF (SD)	1	1.00 (0.07)	0.92 (0.06)	0.94 (0.06)	0.88 (0.05)
95% CrI	-	(0.88, 1.14)	(0.82, 1.03)	(0.84, 1.05)	(0.81, 0.96)
MeanHR (SD)	1	1.01 (0.12)	0.87 (0.09)	0.90 (0.09)	0.80 (0.07)
95% CrI	-	(0.81, 1.24)	(0.72, 1.05)	(0.74, 1.08)	(0.69, 0.93)
Pr(HR < 1)	-	50.60%	93.70%	89.60%	99.00%
Hemorrhagic stroke	100	42	58	56	176
<b>Model 0</b>					
Mean AF (SD)	1	1.03 (0.17)	0.85 (0.12)	0.87 (0.13)	0.98 (0.11)
95% CrI	-	(0.74, 1.38)	(0.63, 1.12)	(0.65, 1.14)	(0.78, 1.22)
MeanHR (SD)	1	1.03 (0.19)	0.82 (0.14)	0.84 (0.15)	0.97 (0.13)
95% CrI	-	(0.70, 1.46)	(0.56, 1.14)	(0.60, 1.17)	(0.75, 1.26)
Pr(HR < 1)	-	47.20%	88.40%	86.30%	63.10%
<b>Model 1</b>					
Mean AF (SD)	1	1.08 (0.17)	0.91 (0.13)	0.92 (0.13)	0.90 (0.10)
95% CrI	-	(0.80, 1.45)	(0.70, 1.20)	(0.71, 1.19)	(0.74, 1.11)
MeanHR (SD)	1	1.11 (0.21)	0.88 (0.16)	0.90 (0.16)	0.88 (0.12)
95% CrI	-	(0.75, 1.58)	(0.63, 1.25)	(0.63, 1.24)	(0.67, 1.14)
Pr(HR < 1)	-	31.60%	79.70%	76.60%	87.60%
<b>Model 2</b>					
Mean AF (SD)	1	1.11 (0.18)	0.93 (0.15)	0.96 (0.16)	0.96 (0.13)
95% CrI	-	(0.79, 1.58)	(0.70, 1.25)	(0.71, 1.34)	(0.76, 1.25)
MeanHR (SD)	1	1.14 (0.22)	0.92 (0.17)	0.95 (0.18)	0.95 (0.14)
95% CrI	-	(0.75, 1.61)	(0.63, 1.29)	(0.65, 1.37)	(0.71, 1.27)
Pr(HR < 1)	-	28.80%	72.40%	64.40%	69.30%
Cerebral infarction	151	41	64	66	198
<b>Model 0</b>					
Mean AF (SD)	1	0.76 (0.09)	0.71 (0.07)	0.74 (0.08)	0.79 (0.06)
95% CrI	-	(0.59, 0.94)	(0.58, 0.86)	(0.61, 0.89)	(0.68, 0.93)
MeanHR (SD)	1	0.65 (0.12)	0.59 (0.09)	0.64 (0.09)	0.71 (0.09)
95% CrI	-	(0.46, 0.92)	(0.43, 0.79)	(0.47, 0.85)	(0.56, 0.89)
Pr(HR < 1)	-	99.10%	99.90%	99.70%	99.50%
<b>Model 1</b>					
Mean AF (SD)	1	0.83 (0.08)	0.79 (0.07)	0.82 (0.07)	0.74 (0.05)
95% CrI	-	(0.68, 1.01)	(0.67, 0.93)	(0.69, 0.96)	(0.66, 0.84)
MeanHR (SD)	1	0.73 (0.13)	0.65 (0.10)	0.70 (0.11)	0.58 (0.07)
95% CrI	-	(0.49, 1.02)	(0.48, 0.88)	(0.51, 0.94)	(0.46, 0.72)
Pr(HR < 1)	-	96.90%	99.80%	98.90%	100.00%
<b>Model 2</b>					
Mean AF (SD)	1	0.84 (0.09)	0.80 (0.08)	0.83 (0.08)	0.75 (0.06)
95% CrI	-	(0.67, 1.02)	(0.67, 0.95)	(0.69, 0.99)	(0.66, 0.85)
MeanHR (SD)	1	0.73 (0.14)	0.67 (0.11)	0.72 (0.12)	0.61 (0.08)
95% CrI	-	(0.50, 1.04)	(0.48, 0.91)	(0.52, 0.99)	(0.48, 0.79)
Pr(HR < 1)	-	96.10%	99.10%	97.50%	99.80%

Note:

Abbreviations: SD, standard deviation; CrI, credible interval; MCSE, Monte Carlo Standard Error;

Pr(HR < 1) indicates the probability for posterior HR to be smaller than 1.

Model 0 = Crude model; Model 1 = age-adjusted model; Model 2 = multivariable adjusted model.

Covariates included in Model 2: age, smoking habit, alcohol intake, body mass index, history of hypertension, diabetes, kidney/liver diseases, exercise, sleep duration, coffee intake, education level.

**Table 3.** Summary of posterior Hazard Ratios (HR) of mortality from total stroke, different stroke type according to the frequency of milk intake in women (JACC study, 1988-2009).

	Never	1-2 times/Month	1-2 times/Week	3-4 times/Week	Almost Daily
Person-year	173222	59904	129233	139919	418925
N	10407	3640	7590	8108	25254
Total Stroke	300	84	182	172	585
<b>Model 0</b>					
MeanHR (SD)	1	0.83 (0.10)	0.81 (0.08)	0.70 (0.07)	0.81 (0.07)
95% CrI	-	(0.64, 1.05)	(0.68, 0.97)	(0.58, 0.85)	(0.71, 0.93)
MCSE	-	0.0029	0.0022	0.0021	0.0023
Pr(HR < 1)	-	94.6%	98.7%	99.9%	99.6%
<b>Model 1</b>					
MeanHR (SD)	1	1.00 (0.14)	1.18 (0.14)	1.03 (0.12)	0.92 (0.09)
95% CrI	-	(0.76, 1.31)	(0.95, 1.47)	(0.82, 1.28)	(0.78, 1.09)
MCSE	-	0.0038	0.0045	0.0042	0.0034
Pr(HR < 1)	-	52.3%	6.3%	42.0%	86.8%
<b>Model 2</b>					
MeanHR (SD)	1	1.01 (0.17)	1.19 (0.15)	1.03 (0.15)	0.95 (0.12)
95% CrI	-	(0.75, 1.36)	(0.96, 1.52)	(0.81, 1.31)	(0.80, 1.17)
MCSE	-	0.0083	0.0096	0.0079	0.0075
Pr(HR < 1)	-	52.8%	6.4%	44.4%	78.0%
Hemorrhagic stroke	108	27	78	76	231
<b>Model 0</b>					
MeanHR (SD)	1	0.73 (0.16)	0.98 (0.15)	0.87 (0.14)	0.89 (0.11)
95% CrI	-	(0.47, 1.08)	(0.71, 1.31)	(0.64, 1.16)	(0.71, 1.15)
MCSE	-	0.0058	0.0071	0.0061	0.0065
Pr(HR < 1)	-	94.7%	58.1%	83.1%	83.0%
<b>Model 1</b>					
MeanHR (SD)	1	0.84 (0.18)	1.17 (0.18)	1.06 (0.17)	0.93 (0.12)
95% CrI	-	(0.54, 1.24)	(0.86, 1.58)	(0.76, 1.45)	(0.73, 1.19)
MCSE	-	0.0065	0.0089	0.0084	0.0069
Pr(HR < 1)	-	81.6%	16.9%	38.9%	74.6%
<b>Model 2</b>					
MeanHR (SD)	1	0.85 (0.18)	1.21 (0.18)	1.13 (0.17)	1.03 (0.12)
95% CrI	-	(0.56, 1.30)	(0.90, 1.62)	(0.84, 1.52)	(0.81, 1.29)
MCSE	-	0.0051	0.0067	0.0039	0.0047
Pr(HR < 1)	-	79.6%	12.7%	33.4%	71.4%
Cerebral infarction	102	35	63	50	187
<b>Model 0</b>					
MeanHR (SD)	1	1.01 (0.13)	0.82 (0.14)	0.59 (0.14)	0.76 (0.16)
95% CrI	-	(0.69, 1.48)	(0.60, 1.13)	(0.43, 0.84)	(0.59, 0.99)
MCSE	-	0.0087	0.0079	0.0064	0.0071
Pr(HR < 1)	-	51.9%	75.6%	97.6%	96.1%
<b>Model 1</b>					
MeanHR (SD)	1	1.29 (0.14)	1.15 (0.13)	0.86 (0.14)	0.86 (0.15)
95% CrI	-	(0.88, 1.89)	(0.84, 1.58)	(0.61, 1.20)	(0.67, 1.09)
MCSE	-	0.0071	0.0072	0.0095	0.0054
Pr(HR < 1)	-	36.7%	42.1%	78.7%	88.9%
<b>Model 2</b>					
MeanHR (SD)	1	1.30 (0.11)	1.18 (0.09)	0.87 (0.10)	0.93 (0.07)
95% CrI	-	(0.88, 1.92)	(0.86, 1.63)	(0.62, 1.23)	(0.72, 1.19)
MCSE	-	0.0055	0.0057	0.0067	0.0047
Pr(HR < 1)	-	35.1%	39.9%	75.6%	80.1%

Note:

Abbreviations: SD, standard deviation; CrI, credible interval; MCSE, Monte Carlo Standard Error;

Pr(HR < 1) indicates the probability for posterior HR to be smaller than 1.

Model 0 = Crude model; Model 1 = age-adjusted model; Model 2 = multivariable adjusted model.

Covariates included in Model 2: age, smoking habit, alcohol intake, body mass index, history of hypertension, diabetes, kidney/liver diseases, exercise, sleep duration, coffee intake, education level.