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

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Abstract: The aim was to further examine the relationship between milk intake and stroke mortality among the Japanese population. We used data from the Japan Collaborative Cohort (JACC) Study to estimate the posterior acceleration factors (AF) as well as the hazard ratios (HR) comparing individuals with different milk intake frequencies against those who never consumed milk at the study baseline. These estimations were computed through a series of Bayesian survival models that employed a Markov Chain Monte Carlo simulation process. 100000 posterior samples were generated separately through four independent chains after model convergency were confirmed. Posterior probabilites that daily milk consumers had lower hazard or delayed mortality from strokes compared to non-consumers was 99.0% and 78.0% for men and women, respectively. Accordingly, the estimated posterior means of AF and HR for daily milk consumers were 0.88 (95% Credible Interval, CrI: 0.81, 0.96) and 0.80 (95% CrI: 0.69, 0.93) for men and 0.97 (95% CrI: 0.88, 1.10) and 0.95 (95% CrI: 0.80, 1.17) for women. In conclusion, data from the JACC study has provided strong evidence that daily milk intake among Japanese men was associated with delayed and lower hazard of mortality from stroke especially cerebral infarction.

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

1. Introduction

Eastern Asian populations were reported to have higher burden from either mortality or morbidity from stroke than populations in European or American regions [1]. Dairy food, especially milk has been suggested to reduce stroke risk by nearly 7% for each 200 g increment of daily consumption [2]. Although 2 daily servings of milk or dairy products is recommended in Japan [3], the actual per capita intake ($\approx$ 63 g/day) of these food groups is much lower and less frequent than that in Western countries [4]. Given that previous reports have also indicated no significant [5–7] or even positive associations [8], it would be of interest to provide information on the association within a context that most individuals have much lower range of milk intake compared to most of the previous studies. Whether people with such a low level intake of milk can still benefit against stroke would require elucidation.

Moreover, a more intuitive interpretation would be available if we were able to show the probabilities and how certain the existing data can provide evidence about whether drinking milk can delay or lower the hazard of dying from stroke. Accelerated failure time models (AFT) under Bayesian framework are convenient tools that would help avoid worrying about the assumption of proportional hazard normally required in a Cox proportional hazard model. AFT model is also helpful in estimating acceleration factors in addition to hazard ratios which can be interpreted as the speed for developing an event of interest. This speed parameter shows how faster/slower individuals in one exposure group might have an event compared to others among different exposure groups [9,10]. AFT models

Our aim was to provide a more straightforward answer to the primary 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 a stroke mortality 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 [11–13]. 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 Hokkaido 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) [14]. From the validation study [14] of the FFQ, daily consumers of milk was found to have a median intake of 146 gram per day.

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

Analyses were stratified by sex as difference in milk consumption levels and mortality rate was suggested previously [15,16]. We calculated sex-specific means (standard deviation, sd) and proportion of selected baseline characteristics according to the frequency of milk intake. Age-adjusted stroke mortality rate were expressed as per 1000 person-year predicted through poisson regression models.

Full parametric proportional hazard models under Bayesian framework with Weibull distribution were fitted using Just Another Gibbs Sampler (JAGS) program [17] version 4.3.0 in R version 4.0.1 [18]. JAGS program is similar to the OpenBUGS [19] 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 [20] 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 $Pr(\text{HR} < 1)$.

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, ≥ 18.5 and < 25, ≥ 25 and < 30, ≥ 30 kg/m^2), history of hypertension, diabetes, kidney/liver diseases (yes/no), exercise (more than 1 hour/week, yes/no), sleep duration (< 7, ≥ 7 and < 8, ≥ 8 and < 9, ≥ 9, hours), quartiles of total energy intake, coffee intake (never, $<$ 3-4 times/week, almost daily), and 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). Age-adjusted stroke mortality rates for each category of milk intake frequency was estimated to be 1.8, 2.0, 1.7, 1.6, 1.5 per 1000 person-year for men and 1.3, 1.4, 1.2, 1.1, 1.2 per 1000 person-year for 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 both sexes.

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 slower speed and lower hazard of dying from total stroke in crude models. Velocities that milk consumers dying from stroke is slower by a crude acceleration factor (AF) between 0.79 (sd = 0.05; 95% CrI: 0.74, 0.90) and 0.93 (sd = 0.04; 95% CrI: 0.85, 1.02) compared with non-consumers. Chances that the posterior crude 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 greater than 94.6% in women. However, lower hazard and delayed

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

	Never	Drinkers	Milk drinkers			
			1-2 times/ Month	1-2 times/ Week	3-4 times/ Week	Almost Daily
Men (n = 39386)						
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)
Current smoker, %	58.7	49.8	57.4	55.9	51.1	45.4
Daily alcohol drinker, %	51.9	47.8	50.9	48.4	48.6	46.5
BMI, kg/m^2 (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)
Exercise (> 1h/week), %	19.0	27.6	26.5	25.0	25.5	29.5
Sleep duration, 8-9 hours, %	35.6	35.9	34.6	36.2	35.1	36.3
Energy intake, kcal/day (mean (SD))	1611 (505)	1764 (504)	1606 (496)	1679 (495)	1772 (509)	1830 (495)
Vegetable intake, daily, %	21.3	25.4	20.1	20.4	20.8	30.1
Fruit intake, daily, %	14.8	22.4	15.4	16.3	17.3	28.1
Green tea intake, daily, %	76.5	79.2	79.9	78.3	77.9	79.8
Coffee intake, daily, %	43.8	50.7	50.5	48.0	47.5	52.9
Educated over 18 years old, %	9.9	14.1	12.4	12.8	11.1	15.9
History of diabetes, %	5.0	6.3	4.5	4.2	5.5	7.7
History of hypertension, %	18.4	17.9	17.5	17.1	16.8	18.7
History of kidney diseases, %	3.0	3.4	3.8	3.0	3.0	3.5
History of liver diseases, %	5.8	6.5	6.3	6.0	5.4	7.2
Women (n = 54999)						
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)
Current smoker, %	6.9	4.2	6.1	5.5	4.3	3.5
Daily alcohol drinker, %	4.3	4.5	5.5	4.3	4.2	4.6
BMI, kg/m^2 (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)
Exercise (> 1h/week), %	13.6	20.8	17.1	18.5	18.8	22.6
Sleep duration, 8-9 hours, %	27.7	25.6	25.1	25.9	25.4	25.7
Energy intake, kcal/day (mean (SD))	1519 (451)	1690 (449)	1522 (447)	1596 (443)	1661 (432)	1752 (443)
Vegetable intake, daily, %	24.7	30.4	25.0	24.6	24.2	34.8
Fruit intake, daily, %	25.0	35.7	26.6	29.2	29.2	41.1
Green tea intake, daily, %	73.8	76.8	77.0	76.4	75.8	77.3
Coffee intake, daily, %	39.6	48.2	46.2	46.4	44.4	50.2
Educated over 18 years old, %	4.8	8.3	6.7	7.2	6.5	9.4
History of diabetes, %	2.6	3.7	3.2	2.7	2.7	4.4
History of hypertension, %	21.5	19.7	20.5	19.1	18.9	20.0
History of kidney diseases, %	3.6	4.1	3.9	3.7	3.7	4.4
History of liver diseases, %	3.5	4.6	4.9	3.9	3.9	5.0

time-to-event was observed to remain after age or multivariable adjustment only among daily male milk consumers. Specifically, the mean (sd; 95% CrI) of posterior multivariable-adjusted AF and HR for daily male consumers of milk were 0.88 (sd = 0.05; 95% CrI: 0.81, 0.96) and 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 AFs and HRs that were distributed with means of 0.97 (sd = 0.09; 95% CrI: 0.88, 1.10) and 0.95 (sd = 0.12; 95% CrI: 0.80, 1.17) which had about 78.0% of chance that their HRs could be smaller than 1.

Posterior distributions of AFs and 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 17%-20% slower velocity or 28%-39% lower hazard of dying from cerebral infarction compared to men who never drank milk (Model 2 in **Table** 2). Probability that the posterior HRs distributed below the null value was greater or equal to 97.5%. No evidence was found about the associations between milk intake and hazard of cerebral infarction mortality among women.

4. Discussion

In the JACC study cohort, our analyses showed that men in Japan who consumed milk almost daily had lower hazard of dying from stroke especially from cerebral infarction. Our evidence also suggested that stroke mortality events were delayed among Japanese male daily milk consumers compared with non-consumers.

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
Model 0					
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)
Mean HR (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)	-	86.5%	99.9%	99.7%	93.5%
Model 1					
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)
Mean HR (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)	-	58.7%	97.3%	96.1%	100.0%
Model 2					
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)
Mean HR (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)	-	50.6%	93.7%	89.6%	99.0%
Hemorrhagic stroke	100	42	58	56	176
Model 0					
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)
Mean HR (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)	-	47.2%	88.4%	86.3%	63.1%
Model 1					
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)
Mean HR (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)	-	31.6%	79.7%	76.6%	87.6%
Model 2					
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)
Mean HR (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)	-	28.8%	72.4%	64.4%	69.3%
Cerebral infarction	151	41	64	66	198
Model 0					
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)
Mean HR (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)	-	99.1%	99.9%	99.7%	99.5%
Model 1					
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)
Mean HR (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)	-	96.9%	99.8%	98.9%	100.0%
Model 2					
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)
Mean HR (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)	-	96.1%	99.1%	97.5%	99.8%

Note:
Abbreviations: N, number of subjects, SD, standard deviation; CrI, credible interval.
Pr(HR < 1) indicates the prabability 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, quartiles of total energy intake, coffee intake, and education level.

Table 3. Summary of posterior Acceleration Factors (AF) and Hazard Ratios (HR) of mortality from total stroke, 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
Model 0					
Mean AF (SD)	1	0.88 (0.07)	0.87 (0.05)	0.79 (0.05)	0.88 (0.04)
95% CrI	-	(0.75, 1.03)	(0.78, 0.98)	(0.71, 0.90)	(0.80, 0.96)
Mean HR (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)
Pr(HR < 1)	-	94.6%	98.7%	99.9%	99.6%
Model 1					
Mean AF (SD)	1	0.99 (0.09)	1.11 (0.08)	1.02 (0.08)	0.95 (0.06)
95% CrI	-	(0.85, 1.17)	(0.97, 1.26)	(0.89, 1.16)	(0.86, 1.06)
Mean HR (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)
Pr(HR < 1)	-	52.3%	6.3%	42.0%	86.8%
Model 2					
Mean AF (SD)	1	1.01 (0.12)	1.11 (0.14)	1.02 (0.12)	0.97 (0.09)
95% CrI	-	(0.85, 1.20)	(0.97, 1.30)	(0.89, 1.19)	(0.88, 1.10)
Mean HR (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)
Pr(HR < 1)	-	52.8%	6.4%	44.4%	78.0%
Hemorrhagic stroke	108	27	78	76	231
Model 0					
Mean AF (SD)	1	0.78 (0.13)	0.98 (0.12)	0.90 (0.11)	0.92 (0.09)
95% CrI	-	(0.55, 1.06)	(0.76, 1.25)	(0.70, 1.13)	(0.76, 1.12)
Mean HR (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)
Pr(HR < 1)	-	94.7%	58.1%	83.1%	83.0%
Model 1					
Mean AF (SD)	1	0.88 (0.13)	1.12 (0.13)	1.04 (0.13)	0.95 (0.09)
95% CrI	-	(0.63, 1.17)	(0.90, 1.41)	(0.82, 1.32)	(0.80, 1.14)
Mean HR (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)
Pr(HR < 1)	-	81.6%	16.9%	38.9%	74.6%
Model 2					
Mean AF (SD)	1	0.93 (0.24)	1.23 (0.38)	1.14 (0.33)	1.04 (0.25)
95% CrI	-	(0.64, 1.33)	(0.93, 1.98)	(0.87, 1.83)	(0.83, 1.55)
Mean HR (SD)	1	0.89 (0.22)	1.26 (0.26)	1.15 (0.23)	1.02 (0.19)
95% CrI	-	(0.55, 1.39)	(0.90, 1.90)	(0.83, 1.74)	(0.78, 1.51)
Pr(HR < 1)	-	73.2%	9.5%	24.8%	53.3%
Cerebral infarction	102	35	63	50	187
Model 0					
Mean AF (SD)	1	1.01 (0.13)	0.90 (0.09)	0.75 (0.08)	0.86 (0.06)
95% CrI	-	(0.79, 1.27)	(0.75, 1.10)	(0.60, 0.91)	(0.75, 0.99)
Mean HR (SD)	1	1.03 (0.20)	0.85 (0.14)	0.61 (0.11)	0.78 (0.10)
95% CrI	-	(0.69, 1.48)	(0.60, 1.13)	(0.43, 0.84)	(0.59, 0.99)
Pr(HR < 1)	-	51.9%	75.6%	97.6%	96.1%
Model 1					
Mean AF (SD)	1	1.21 (0.32)	1.16 (0.30)	0.98 (0.19)	0.97 (0.14)
95% CrI	-	(0.95, 2.08)	(0.93, 1.95)	(0.79, 1.48)	(0.84, 1.43)
Mean HR (SD)	1	1.37 (0.33)	1.25 (0.28)	0.94 (0.22)	0.92 (0.17)
95% CrI	-	(0.89, 2.18)	(0.87, 1.95)	(0.63, 1.52)	(0.69, 1.40)
Pr(HR < 1)	-	8.5%	14.2%	70.1%	79.4%
Model 2					
Mean AF (SD)	1	1.19 (0.19)	1.12 (0.15)	0.96 (0.12)	0.97 (0.09)
95% CrI	-	(0.94, 1.62)	(0.92, 1.49)	(0.78, 1.21)	(0.83, 1.18)
Mean HR (SD)	1	1.38 (0.29)	1.21 (0.22)	0.91 (0.18)	0.94 (0.14)
95% CrI	-	(0.89, 2.02)	(0.85, 1.70)	(0.62, 1.34)	(0.69, 1.25)
Pr(HR < 1)	-	7.3%	15.6%	72.8%	70.0%

Note:
Abbreviations: N, number of subjects, SD, standard deviation; CrI, credible interval.
Pr(HR < 1) indicates the prabability 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, quartiles of total energy intake, coffee intake, and education level.

These findings showed similar negative effect estimates reported previously [15] using data from the same cohort, in which the outcomes of interests were focused on cardiovascular diseases and all-cause mortality. Moreover, we have further updated the results with more comprehensive and straightforward evidence about whether and how certain the data had shown about daily consumption of milk is contributing to a postponed stroke (mostly cerebral infarction) mortality event among Japanese men. A recent dose-response meta-analysis of 18 prospective cohort studies had shown a similar negative association [2] between milk consumption and risk of stroke. The same meta-analysis also reported a greater reduction of risk of stroke (18%) for East Asian population in contrast with the 7% less risk in the pooled overall finding for all populations combined. Benefits of increased milk intake might be particularly noticeable in East Asian countries where strokes are relatively more common, and milk consumption is much lower than those studies conducted among European or American populations [21]. However, the Life Span Study [6], which was conducted about 10 years earlier than the JACC Study, reported null association between milk intake and fatal stroke among men and women combined who survived from the Hiroshima and Nagasaki atomic bomb. The difference could be largely explained by the different targeting populations between the two studies. Kondo *et al.* [22] also reported null association in either men or women from the NIPPON DATA80 study. In fact, the exact number of stroke mortality events was about 85% less and the number of participants in the NIPPON DATA80 was about 90% less than those in the JACC study database, their null association might likely due to its limited statistical power. Umesawa *et al.* [23] reported that dairy calcium intake was inversely associated with ischemic stroke mortality risk which could be considered as one of the potential evidence that supported our findings. Furthermore, stronger inverse association between milk consumption and stroke mortality in men rather than in women was found in the Singapore Chinese Health Study [16] as well. The reasons for this gender differences is currently unknown. It might be contributed by generally better/healthier lifestyles (much less smokers and alcohol drinkers) in women regardless of milk intake frequency, or maybe due to other factors that was not available in/considered by our models such as intake of calcium supplements. The probably existing beneficial effect by milk intake is probably less evident in women than that in men. Further investigation is needed.

Possible reasons for a protective effect of milk consumption against stroke could be interpreted as such an association may be mediated by its content in calcium, magnesium, potassium, and other bioactive compounds, as recommended by Iacoviello *et al.* [24]. Apart from the inorganic minerals in milk that would be helpful with health effects, recent studies on animal models also indicated key evidence that stroke-associated morbidity was delayed in stroke-prone rats who were fed with milk-protein enriched diets [25,26]. More precisely, Singh *et al.* [27] found that whey protein and its components lactalbumin and lactoferrin improved energy balance and glycemic control against the onset of neurological deficits associated with stroke. Bioactive peptides from milk proteins were also responsible for limitation of thrombosis [28] through their angiotensin convertase enzyme inhibitory potential, which might partly explain why the effect was found mainly for mortality from cerebral infarction in the current study.

4.1. Strength and limitations

Some limitations here are worth mentioning. First, the milk intake frequency as well as other lifestyle information was collected only once at the baseline and was self-reported. Apparently life habits are possible to alter over time and these would resulted in misclassfication and residual confoundings. Second, despite reasonable validity of FFQ in the JACC study cohort was assessed and confirmed, measurement errors are inevitable. Therefore, we did not try to compute the amount of consumption by multiplying an average volume per occasion with the frequency of intake since the random error might be exaggerated and the observed associations may have attenuated. Strengths of our analyses included that we have transformed the research questions to more transparent ones that is easier for interpretation. Direct probabilities that daily milk intake is associated with lower hazard or delayed stroke mortality event were provided here after thorough computer simulations.

4.2. Conclusion

In conclusion, the JACC study database has provided evidence that Japanese men who consumed milk daily had lower hazard of dying from stroke particularly cerebral infarction compared with their counterparts who never consumed milk. Time before an event of stroke mortality occurred were slowed down and delayed among men who drank milk regularly.

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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

References

1. Kim, J.S. Stroke in Asia: a global disaster. *International Journal of Stroke* **2014**, *9*, 856–857.
2. De Goede, J.; Soedamah-Muthu, S.S.; Pan, A.; Gijsbers, L.; Geleijnse, J.M. Dairy consumption and risk of stroke: a systematic review and updated dose–response meta-analysis of prospective cohort studies. *Journal of the American Heart Association* **2016**, *5*, e002787.
3. Yoshiike, N.; Hayashi, F.; Takemi, Y.; Mizoguchi, K.; Seino, F. A new food guide in Japan: the Japanese food guide Spinning Top. *Nutrition reviews* **2007**, *65*, 149–154.
4. Saito, A.; Okada, E.; Tarui, I.; Matsumoto, M.; Takimoto, H. The Association between Milk and Dairy Products Consumption and Nutrient Intake Adequacy among Japanese Adults: Analysis of the 2016 National Health and Nutrition Survey. *Nutrients* **2019**, *11*, 2361.
5. Iso, H.; Stampfer, M.J.; Manson, J.E.; Rexrode, K.; Hennekens, C.H.; Colditz, G.A.; Speizer, F.E.; Willett, W.C. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. *Stroke* **1999**, *30*, 1772–1779.
6. Sauvaget, C.; Nagano, J.; Allen, N.; Grant, E.J.; Beral, V. Intake of animal products and stroke mortality in the Hiroshima/Nagasaki Life Span Study. *International Journal of Epidemiology* **2003**, *32*, 536–543.

7. Elwood, P.C.; Pickering, J.E.; Fehily, A.; Hughes, J.; Ness, A. Milk drinking, ischaemic heart disease and ischaemic stroke I. Evidence from the Caerphilly cohort. *European journal of clinical nutrition* **2004**, *58*, 711–717.
8. Larsson, S.C.; Männistö, S.; Virtanen, M.J.; Kontto, J.; Albanes, D.; Virtamo, J. Dairy foods and risk of stroke. *Epidemiology (Cambridge, Mass.)* **2009**, *20*, 355.
9. Wei, L.J. The accelerated failure time model: a useful alternative to the Cox regression model in survival analysis. *Statistics in Medicine* **1992**, *11*, 1871–1879.
10. Ibrahim, J.G.; Chen, M.H.; Sinha, D. Bayesian Survival Analysis. *Wiley StatsRef: Statistics Reference Online* **2014**.
11. Ohno, Y.; Tamakoshi, A.; Group, J.S.; others. Japan collaborative cohort study for evaluation of cancer risk sponsored by monbusho (JACC study). *Journal of Epidemiology* **2001**, *11*, 144–150.
12. Tamakoshi, A.; Yoshimura, T.; Inaba, Y.; Ito, Y.; Watanabe, Y.; Fukuda, K.; Iso, H. Profile of the JACC study. *Journal of Epidemiology* **2005**, *15*, S4–S8.
13. Tamakoshi, A.; Ozasa, K.; Fujino, Y.; Suzuki, K.; Sakata, K.; Mori, M.; Kikuchi, S.; Iso, H. Cohort profile of the Japan Collaborative Cohort Study at final follow-up. *Journal of Epidemiology* **2013**, p. JE20120161.
14. Date, C.; Fukui, M.; Yamamoto, A.; Wakai, K.; Ozeki, A.; Motohashi, Y.; Adachi, C.; Okamoto, N.; Kurosawa, M.; Tokudome, Y.; others. Reproducibility and validity of a self-administered food frequency questionnaire used in the JACC study. *Journal of Epidemiology* **2005**, *15*, S9–S23.
15. Wang, C.; Yatsuya, H.; Tamakoshi, K.; Iso, H.; Tamakoshi, A. Milk drinking and mortality: findings from the Japan collaborative cohort study. *Journal of Epidemiology* **2015**, *25*, 66–73.
16. Talaei, M.; Koh, W.P.; Yuan, J.M.; Pan, A. The association between dairy product intake and cardiovascular disease mortality in Chinese adults. *European Journal of Nutrition* **2016**, *56*, 2343–2352. doi:10.1007/s00394-016-1274-1.
17. Plummer, M. JAGS: A program for analysis of Bayesian graphical models using Gibbs sampling, 2003.
18. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria, 2020.
19. Lunn, D.; Spiegelhalter, D.; Thomas, A.; Best, N. The BUGS project: Evolution, critique and future directions. *Statistics in Medicine* **2009**, *28*, 3049–3067.
20. Brooks, S.P.; Gelman, A. General methods for monitoring convergence of iterative simulations. *Journal of Computational and Graphical Statistics* **1998**, *7*, 434–455.
21. Dehghan, M.; Mente, A.; Rangarajan, S.; Sheridan, P.; Mohan, V.; Iqbal, R.; Gupta, R.; Lear, S.; Wentzel-Viljoen, E.; Avezum, A.; others. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. *The Lancet* **2018**, *392*, 2288–2297.
22. Kondo, I.; Ojima, T.; Nakamura, M.; Hayasaka, S.; Hozawa, A.; Saitoh, S.; Ohnishi, H.; Akasaka, H.; Hayakawa, T.; Murakami, Y.; others. Consumption of dairy products and death from cardiovascular disease in the Japanese general population: the NIPPON DATA80. *Journal of Epidemiology* **2013**, *23*, 47–54.
23. Umesawa, M.; Iso, H.; Ishihara, J.; Saito, I.; Kokubo, Y.; Inoue, M.; Tsugane, S. Dietary calcium intake and risks of stroke, its subtypes, and coronary heart disease in Japanese: the JPHC Study Cohort I. *Stroke* **2008**, *39*, 2449–2456.
24. Iacoviello, L.; Bonaccio, M.; Cairella, G.; Catani, M.V.; Costanzo, S.; D'Elia, L.; Giacco, R.; Rendina, D.; Sabino, P.; Savini, I.; others. Diet and primary prevention of stroke: Systematic review and dietary recommendations by the ad hoc Working Group of the Italian Society of Human Nutrition. *Nutrition, Metabolism and Cardiovascular Diseases* **2018**, *28*, 309–334.
25. Chiba, T.; Itoh, T.; Tabuchi, M.; Ooshima, K.; Satou, T.; Ezaki, O. Delay of stroke onset by milk proteins in stroke-prone spontaneously hypertensive rats. *Stroke* **2012**, *43*, 470–477.
26. Singh, A.; Pezeshki, A.; Zapata, R.C.; Yee, N.J.; Knight, C.G.; Tuor, U.I.; Chelikani, P.K. Diets enriched in whey or casein improve energy balance and prevent morbidity and renal damage in salt-loaded and high-fat-fed spontaneously hypertensive stroke-prone rats. *The Journal of nutritional biochemistry* **2016**, *37*, 47–59.
27. Singh, A.; Zapata, R.C.; Pezeshki, A.; Knight, C.G.; Tuor, U.I.; Chelikani, P.K. Whey Protein and Its Components Lactalbumin and Lactoferrin Affect Energy Balance and Protect against Stroke Onset and

Renal Damage in Salt-Loaded, High-Fat Fed Male Spontaneously Hypertensive Stroke-Prone Rats. *The Journal of Nutrition* **2020**, *150*, 763–774.

28. Tokajuk, A.; Zakrzeska, A.; Chabielska, E.; Car, H. Whey protein concentrate limits venous thrombosis in rats. *Applied Physiology, Nutrition, and Metabolism* **2019**, *44*, 907–910.