

Response to the reviewers

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

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We appreciate the reviewers for their helpful comments. We have incorporated them in the revised manuscript. Please find below a detailed point-by-point responses to all comments. In the tracked changes manuscript, we provided the LaTeX diff file so that changes made can easily be identified. A clean file without tracked changes was also included.

Comment from reviewer #1

Thank you very much to the Editorial for entrusting me with the task of reviewing the article. The manuscript presented for review raises a very important health problem, which is stroke. Stroke continues to be one of the leading causes of death and disability in adults. It is a significant health problem which contributes significantly to reduce the quality of life. The key issue from the medical and social point of view remains effective primary and secondary prevention. The current state of knowledge indicates a significant and constantly growing importance non-pharmacological activities undertaken as part of primary prevention stroke, representing a complementary for drug therapy and just as important area of intervention. The broadly understood “primary prevention” has to be implementing it at an early stage, raising awareness of health care professionals and patients.

It is known that what you eat can increase or decrease your risk of stroke. The relationship between milk intake and stroke mortality is very interesting and it has a practical effect. The authors of the presented manuscript, as well as other researchers, observed that higher milk consumption is also associated with a healthier diet, greater physical activity and not smoking.

The summary actually shows the problem at hand.

The work structure is correct. Most sections are clearly and accurately described.

Tables are legible and correctly described.

The writings cited by the authors are up-to-date and appropriate.

Minor revision:

I would make a clearer and separate section for “Conclusions” and “Study limitations”.

Congratulations to the authors of the interestingly described research on a large group of participants.

[Response:] We really appreciate the reviewer for the positive comments. We have updated the manuscript with separated sections for study limitations and conclusions.

Comments from reviewer #2

The manuscript by C Wang et al includes a cohort of 94385 men and women from Japan, free from self-reported history of stroke, cancer, myocardial infarction and other types of heart disease at baseline who answered an FFQ regarding milk consumption. Between baseline in 1988-90 and end of follow-up in 2009, 2675 deaths from stroke were recorded on death registers. The authors applied Bayesian survival analysis to calculate hazard ratios and acceleration factors. With a range of milk consumption from “never” to “almost daily”, a higher milk consumption was associated with lower hazard and speed from dying from total stroke among men but not among women.

I have the following comments and questions for the authors:

- #1: The introduction and discussion should however be more clear about the fact that the study is being performed in the lower range of the milk intake distribution. The dose-response meta-analysis in reference 2 indicates that the association may be non-linear. It would be good if the authors in more detail compared their results with other studies using fatal stroke as outcome and perhaps also focus on those cohorts with a low milk intake. For example, please elaborate on references 6, 20-23 in the discussion. Some of the references do not investigate milk intake per se. In the discussion, please specify that reference 19 does not investigate stroke mortality but CVD and all-cause mortality.*

[Response:] We greatly appreciate the reviewer's points. We have updated the Introduction as well as the Discussion so that we could draw readers' attention to the fact that absolute milk intake of these participants were actually in the lower range of milk intake in the world. We have elaborated the issue in Discussion by comparing our findings with previous studies conducted in East Asian population. We have also clarified the fact that the reference #19 in the previous manuscript (#16 in the revised manuscript) dealt with milk intake in relation to CVD and all-cause mortality.

- #2: I am unfortunately not familiar with the Bayesian models used in this work. I am sure that many readers will be in a similar situation as me. I appreciate that these models can calculate hazard ratios without fulfilling the proportional hazards assumption. The authors should in more detail describe the benefits and limitations of these models in relation to the more commonly used Cox proportional hazards regression. Is a HR estimated from these models directly comparable with that from a Cox model? How is an acceleration factor interpreted? Do the models assume that a higher milk intake is associated with a lower stroke mortality, indicated also by the $Pr(HR < 1)$? If so, how would that influence the validity of the method since you in the introduction write that there are reports of inverse associations, no association, and direct associations? In Table 2, both SD and 95% CrI are given. Is there a reason for specifying the SD?*

[Response:] Thanks for the frank comments about the Bayesian models and suggestions. We gave more explanations for the methods as well as benefit and background for their use in the revised manuscript. For example, acceleration factor (AF) can be interpreted as the

speed/velocity just like all individuals are driving their cars from the same start point (entry into the study setting) to their goals (stroke mortality) but different people can drive their own car with different speeds. If the AF of a certain group is smaller than 1 (i.e., reference group - never drinker), then it is considered that individuals in that group would reach the goal with slower speed (or take longer time). We might be able to argue that the statistic AF would be easier to be interpreted compared with hazard ratios (HR), which often requires several assumptions.

We also realized that not many readers would be familiar with the method employed in the present study. In an attempt to briefly introduce the Bayesian approach to the reviewer, we would like to give our understanding of the traditional Cox proportional hazard model (or any other classical statistical methods). First, it assumes only one true but unknown value of the parameter (in this context, the HR and AF) is going to be obtained from the data at hand. Second, it assumes that the experiment/study can be repeated. This is fundamental to the calculation of the confidence intervals through the calculation of standard errors so that they can be interpreted as “if we repeat the same experiment for many times, 95% of these confidence intervals will contain the true but unknown value of interest”. Third and similarly, a P-value is the probability of observing a certain or more extreme results if an experiment/study can be repeated, which would raise a question that relying on $P < 0.05$ criterion may not be valid if the repeatable assumption is not valid.

Instead of employing the unrealistic repeatable assumption, Bayesian ways of statistical analyses provide a posterior distribution of the parameter of interest. In other words, it estimates the a statistic (e.g., HR, AF, etc.) with a distribution that can be described by its mean and standard deviation. And through which the 95% credible intervals can be presented and be interpreted as we are 95% sure that the parameter of interest is distributed in this range. Although Bayesian approach requires extensive simulations, it provides straightforward results, that is, $\Pr(\text{HR} < 1)$, the percentages of observed HRs that were smaller than 1.

We would like to emphasize that the statistical models used in the Bayesian approach is the same as that in the traditional approach. Therefore, the meaning of HRs is the same. One and the biggest drawback of the Bayesian approach is the extensive computational cost, which was partly resolved by the recent advancement of personal computers. Nevertheless, we presented results obtained using the Bayesian approaches in the present study since we believe it is more appropriate statistically. We have added these issues in the “strength and limitation” section of the revised manuscript.

- *#3: Why were analyses performed stratified by sex? Since no pooled analysis is presented, the reason for a stratified analysis should be stated in the aims, unless this was a secondary analysis and then also the results from the total cohort should be presented. The authors should also discuss the observed sex differences in more detail. Do other studies show similar sex differences? What potential biological mechanisms may explain them?*

[Response:] Thanks for the pertinent comment. Although we conducted the presenty analyses in men and women separately from the beginning based our previous finding

from the same cohort as well as on a prior finding from the Singapore Chinese Health Study, the rationale might not have been clear. We have revised the manuscript (Methods) incorporating the point. Nevertheless, a test of interaction for milk intake by sex indicated significant interaction (using traditional likelihood ratio test comparing Cox proportional hazard models with and without the interaction terms between sex and milk intake frequencies, $P < 0.0001$, not shown in the main test). Stratified analyses by sex also suggested the directions of AFs and HRs differ in a few frequency categories (Table 2 and 3, results in the “total stroke” parts).

We have also added possible explanations for the sex-interaction in the Discussion.

- *#4: The aim states to “provide a more straightforward answer to the primary research question” – compared to what? And how is this more straightforward answer achieved. This is not clear, neither in the aim nor in the discussion (lines 166-167). Please revise.*

[Response:] Thanks for the useful suggestion. We meant that the Bayesian approach would provide more straightforward answer compared to traditional statistical approach. We have added clearer descriptions about these research questions and interpretations in Introduction and Discussion.

- *Please describe the context of milk intake in Japan. Is milk consumed as a beverage with food, added to coffee or other consumption patterns? Are other milk products than fresh non-fermented milk consumed and could be included in the “milk” exposure?*

[Response:] We appreciate the reviewer’s great points. During the baseline years of the JACC study (between 1988 and 1990), most “milk and dairy product” consumption (92.1%) was in the form of whole milk. We have added the context of milk intake in Japan for participants who were invited into the JACC study. For detailed description about more current situation, as we cited in the Introduction (Reference #4, as cited below), the per capita consumption is still much lower than that in the western population:

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.

- *Please specify age at baseline in abstract and methods.*

[Response:] Age range are now added in the abstract and methods accordingly.

- *Outcome ascertainment: Information on cause of death was from death certificates. Is there a possibility of individual linkage of the FFQ responses to a cause of death registry or were each of the participants’ death certificates reviewed? How many died from other causes, how many moved from the study area (and were thus lost to follow-up) and how many were censored at the end of follow-up (alive). Has stroke mortality changed during follow-up? Is there a difference in time trends of stroke subtype mortality? In how many cases was stroke subtype not recorded? The authors should also discuss potential reasons for differences in the results for stroke subtypes.*

[Response:] We are grateful to the reviewer's suggestion. We have added these detailed information at the beginning of the Results section. In the study area, investigators conducted systematic review of death certificates till the end of 2009. Date and cause of death were confirmed with the permission of the Director-General of the Prime Minister's Office. Number of deaths from causes other than stroke were 18868 (10731 men and 8137 women); 5493 (2022 men and 3471 women) dropped out from the follow-up (5.8%); 67349 (25281 men and 42068 women) were censored at the end of follow-up (71.4%). Among the 2675 stroke mortality confirmed in the JACC study, 766 were unfortunately not recorded with subtypes. The median (IQR) of follow-up years for cerebral infarction mortality were 11.2 (7.1, 15.3) and 11.8 (7.9, 16.4) in men and women; the median (IQR) of follow-up years for hemorrhagic stroke mortality were 9.9 (5.4, 12.3) and 10.9 (5.9, 15.1) in men and women. Potential reasons for differences in the results for stroke subtypes are described in discussion.

- *I agree with the authors that presenting the results in the FFQ categories is a good option, rather than to calculate the amount of consumption. However, I wonder if there is some indication from the validation study as to how much is on average consumed in the higher categories of intake?*

[Response:] Thanks for the suggestion. The validation study of the FFQ used in the JACC study found that the median intake for a milk consumer was about 146 grams per day. This has been added in the first paragraph of "2.2 Exposure and the outcome of interest" section.

- *Why did you adjust for sleep duration, is that a factor that influences both milk intake and stroke mortality risk?*

[Response:] Thanks for pointing this out. A previous report from the JACC Study (cited as below) showed that healthy lifestyle behaviors are closely related with each other and (including milk intake daily and proper sleep duration) were associated with CVD mortality. Therefore, we also included sleep duration as one of the potential confounders.

Eri Eguchi, Hiroyasu Iso, Naohito Tanabe, Yasuhiko Wada, Hiroshi Yatsuya, Shogo Kikuchi, Yutaka Inaba, Akiko Tamakoshi, on behalf of the Japan Collaborative Cohort Study Group, Healthy lifestyle behaviours and cardiovascular mortality among Japanese men and women: the Japan collaborative cohort study, European Heart Journal, Volume 33, Issue 4, February 2012, Pages 467–477.

- *The manuscript has minor language errors throughout and would benefit from a language review.*

[Response:] Many thanks for your detailed comments that helped us to improve the quality and readability of our manuscript. We tried our best to check and fix the language errors throughout the revised version of the paper.