Author’s response to reviews

Title: Sauna bathing is associated with reduced cardiovascular mortality and improves risk prediction in men and women. A prospective cohort study

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Author’s response to reviews:

Response to comments of editor and reviewers

EDITORIAL COMMENTS

Your manuscript "Sauna bathing is associated with reduced cardiovascular mortality and improves risk prediction in men and women. A prospective cohort study" (BMED-D-18-00870) has been assessed by our reviewers. They have raised a number of points which we believe would improve the manuscript and may allow a revised version to be published in BMC Medicine. In particular, we encourage you to conduct the further analyses suggested by Reviewer 5 (e.g. more explicating dichotomising the cohort into males and females, and by age, and dividing sauna use into finer categories to create more clearly identifiable boundaries), to make the manuscript more impactful.

In addition to addressing the reviewers' comments, please also address the following editorial concerns:

- In your 'Ethics approval and consent to participate' declaration, please add the ethics approval/reference number(s).

- Please add the declaration 'Consent for publication'
A point-by-point response letter must accompany your revised manuscript. This letter must provide a detailed response to each reviewer/editorial point raised, describing exactly what amendments have been made to the manuscript text and where these can be viewed (e.g. Methods section, line 12, page 5). Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes. If you disagree with any comments raised, please provide a detailed rebuttal to help explain and justify your decision.

Please also ensure that your revised manuscript conforms to the journal style, which can be found in the Instructions for Authors on the journal homepage.

RESPONSE: We have enclosed a point-by-point response to all reviewers and editors’ comments and ensured that the revised manuscript conforms to the journal style. Unfortunately, we are unable to split the sauna exposure into finer categories because of the low event rates in the upper categories (please the results).

REVIEWERS’ COMMENTS

Reviewer #1: Hirofumi Tanaka

In this population-based study, Laukkanen et al. investigated the association between sauna bathing and CVD mortality over a period of over 14-years in a sample of middle-aged to elderly men and women in Eastern Finland. The research topic is of growing relevance in the field and worthy of investigation. The manuscript is also well-written and easy to follow.

RESPONSE: Thank you for the compliments.

This study concluded that those who sauna bathe 4-7 times per week for greater than 45 min per week stood to gain the largest benefit in decreased CVD mortality risk. However, group characteristics were not homogenous at baseline which can thus change statistical outcome. The number of men, smokers, alcohol consumption, pervious myocardial infarction, history of coronary heart disease, type 2 diabetes, and hypertension vary across groups. There is no control in this study which makes the Hazard Ratio's less impactful. Instead, the authors used the HRs to compare infrequent sauna users to moderate to heavy sauna users. They stratified the different categories based on questionnaires, but it would have been advantageous for them to maintain a
control group of "0 sessions per week". This may be a result of the Finnish lifestyle as saunas are a normal part of life, but it brings into question the validity of their results. Due to the fact that this study was conducted over a long period of time, how do the researchers know that those classified in the "4-7 sessions per week" group maintained the same behavior over 14 years and vice versa for someone placed in the "0-1 sessions per week" group?

RESPONSE: Thank you for these important comments. The lack of an appropriate control (participants who do not use sauna at all) is an inherent limitation of this study and other previously published studies by our group. Given that sauna bathing is a Finnish tradition and the greater majority of the population have the opportunity to have a sauna bath at least once a week, thus only a handful of people did not use sauna baths at all and therefore we were unable to assess the associations using this group as a reference comparison. This is a well-known characteristic in the Finnish population where sauna use is a very popular activity. Thus, we employed exposure categories to maintain consistency with that of previous reports. To minimize this limitation, however, we conducted a subsidiary analysis which employed a combination of people who did not use sauna baths at all and those who had a single sauna session per week as a reference comparison group. Based on this subsidiary analysis, our main findings were observed to be qualitatively similar.

Page 6, Lines 157-161: “Subjects were classified into groups on the basis of frequency of sauna bathing (1, 2-3 and 4-7 times per week) and the total weekly duration of a sauna bathing (≤15, 16-45, >45 minutes per week), to maintain consistency with previous reports.[6, 8, 19, 30] In a subsidiary analysis, we categorized frequency of sauna bathing into 0-1, 2-3 and 4-7 times per week, including participants who did not use sauna at all (n=43).”

Page 9, Lines 249-251: “In a subsidiary analysis which compared 4-7 sauna sessions per week with 0-1 sauna session per week, the associations were similar (Supplementary Table 3).”

Indeed, sauna bathing habits may have changed during follow-up due to probable changes in health habits or other incident diseases of participants occurring over the long period of time. However, based on findings from studies based on Finnish sauna, any changes may be minimal as sauna habits are fairly stable in the Finnish population. In our revised manuscript, these two important inherent limitations have been emphasized in the limitations section.

Page 12, Lines 351-353: “Sauna bathing habits may have changed during follow-up due to probable changes in health habits or other incident diseases of participants occurring over the long period of time; however, any changes may be minimal as sauna habits are fairly stable in the Finnish population.[30]”
“Secondly, we were unable to assess the associations between sauna bathing and CVD mortality risk when comparing people who used sauna with people who did not use sauna at all (control group). Indeed, majority of Finnish people are accustomed to having a sauna bath regularly at least once per week, as it is traditionally part of Finnish culture.[30, 40] The associations were unchanged in a subsidiary analysis which employed a combination of people who did not use sauna baths and those who had a single sauna session per week as a reference comparison.”

The researchers state that they adjusted the models for given characteristics but did not state how the models were statistically adjusted to be independent of age, sex, disease state, physical activity etc. More detail should be given about the covariate analysis used.

RESPONSE: Our selection of covariates for adjustment was on the basis of their previously established roles as well-defined predictive or confounding factors, evidence from previous research, or their potential as confounders based on known associations with cardiovascular outcomes and observed associations with sauna exposure using the available data. These covariates were also used in other studies in sauna and CVD-related outcomes.

Page 6, Lines 166-169: “Covariates were selected on the basis of their previously established roles as well-defined predictive or confounding factors, evidence from previous research, or their potential as confounders based on known associations with cardiovascular outcomes and observed associations with sauna exposure using the available data.[31]”

We have reported in the statistical analysis section that the results (HRs) were adjusted progressively for age and gender (Model 1); BMI, smoking, systolic blood pressure (SBP), serum low-density lipoprotein cholesterol (LDL-C), alcohol consumption, previous myocardial infarction, and type 2 diabetes (Model 2); total duration of physical activity per week and SES (Model 3); and incident CHD events as a time-varying covariate (Model 4) and have clearly been shown in the tables of results. As we have data on many essential characteristics available, the adjustments were performed as carefully as possible to avoid residual confounding, and the associations between sauna bathing and CVD mortality were independent of these characteristics.

Sensitivity analysis used in the paper excluded the first 5 years of follow-up (Line 22-24). This is ~1/3 of the amount of time that data was collected. The implications of exclusion could have skewed data analysis and created bias. The researchers should explain why there was 5 years of exclusion.
RESPONSE: Thank you for this comment. This sensitivity analysis is commonly employed in epidemiological studies to minimize the possibility that those with underlying disease (but undiagnosed) may have died earlier – the phenomenon of reverse causation bias. By doing so and demonstrating similar results, we have shown that our observed findings are not due to reverse causation bias. This has now been indicated in the statistical analysis section Page 6, Lines 179-180: “To minimize biases due to reverse causation, sensitivity analysis involved excluding the first five years of follow-up.”

We have also mentioned this as a strength of the study and is reported in Page 12, Lines 347-351: “It is possible that underlying diagnosed or undiagnosed diseases may have effect on sauna bathing habits, suggesting reverse causality; however, our subgroup analyses according to various clinical characteristics were consistent and the associations remained robust in several sensitivity analyses, independent of many underlying clinical conditions and exclusion of the first five years of follow-up.”

Since the temperature has a wide range from 80-100 degrees Celsius, the temperature may have had an effect on the duration and frequency of the sauna bathing. Since subjects were classified based on duration and frequency, it is important to question what effect other variables such as temperature may have on the classification system. The researchers did ask the subjects to report temperature in a questionnaire, but since the temperature varied significantly, it should have been measured more carefully. In their reporting, the mean values were 77.1 C for men and 74.7 C for women which do not agree with the 80-100 C range.

RESPONSE: Thank you for these important comments. Assessments of weekly sauna sessions, duration, and temperature in sauna room were based on self-administered questionnaires. Other lifestyle characteristics such as diet, physical activity, sleeping, daily work activities, smoking, and alcohol consumption were also ascertained by self-administered questionnaires. These were then cross-checked by an experienced nurse. Though, there is a possibility of misclassification and recall bias, these methods are well established ways of ascertaining information in observational epidemiological studies of this nature. Finnish saunas have temperature indicators and the temperature of the sauna bath is always noted by the sauna bather before and during the sauna bath. Therefore, the possibility of temperature recall bias is very minimal. Indeed, temperature may have had an influence on the findings. However, we accounted for sauna temperature in further analyses and the associations were observed to persist. We have now included the limitation of the potential for misclassification and recall bias.

Page 12, Lines 339-340: “As with all observational epidemiological studies, exposure assessments based on self-administered questionnaires are prone to misclassification and recall bias.”
It is unclear how this study sample was obtained. Was this data obtained 15+ years ago with the intention of completing a longitudinal observation or was this an older data set that was used for this additional purpose?

RESPONSE: The Kuopio Ischaemic Heart Disease (KIHD) study is a population-based prospective cohort, which was designed to investigate various established and emerging risk factors such as sauna bathing habits and their associations with cardiovascular outcomes. The KIHD study was initially based on a cohort of men aged 42-61 years who were living in Kuopio and the surrounding rural communities in the east of Finland. In the 11-year follow-up of the first cohort, women were invited to join this study so that both genders were available. During participant recruitment, only middle-aged men were included as they were considered to be at high risk for CVDs, with high prevalence and incidence of coronary heart disease, in the area of Eastern Finland and there was an urgent need to study men during these years. However, this presented study is the well-defined cohort including both men and women which is being utilized for this analysis. We have now provided further details in the “study design” section to clarify this.

Page 4, Lines 94-99: “We employed the Kuopio Ischaemic Heart Disease (KIHD) study, which is a population-based prospective cohort study designed to investigate sauna bathing habits and other risk factors for CVD.[19, 20] The KIHD study was initially based on a cohort of men aged 42-61 years who were living in Kuopio and the surrounding rural communities in the east of Finland. In the 11-year follow-up visit of the first cohort, women were invited to join this study. In this cohort which is being utilized for this analysis, participants (n=2358) comprised a randomly selected sample of 1351 women and 1007 men aged 53.4 to 73.8 years.”

How realistic is it to expect people to attend the sauna 4-7 times per week for 45 min per week or greater? Culturally this may make sense for European countries, however, on a large scale in warmer climate areas (South America, United States, etc.) is the feasible? Will people adhere to this ideology?

RESPONSE: Sauna bathing is used for the purposes of relaxation and pleasure and it is an enjoyable experience, whether in warm or cold climates. Therefore, it is not supposed to be a prescription that needs adherence to. The use of sauna is becoming increasing popular in many other continents such as the Americas and the Asian region. This is evidenced by the increasing number of published reports on sauna use from these regions. Page 3, Lines 64-65: “Sauna bathing, a form of passive heat therapy, is a traditional activity in Finland and widely used for relaxation purposes and is becoming increasingly common in many other countries.[1-4]”

We agree that more evidence is needed from other cultures with different kind of saunas and sauna bathing habits, including comparison with the health effects of steam rooms and hot tubes.
Figure 4 is not clear. What are the groups being shown for frequency and duration?

RESPONSE: Figure 4 shows the associations of both frequency and duration of sauna bathing with cardiovascular mortality, by several relevant groups which can be found in the left-hand column of the graph. To avoid plotting two graphs, we merged them into one graph. To make this clearer, we have now plotted individual graphs – Figures 4 and 5.

Reviewer #2: Joel Trinity

The manuscript by Laukkanen entitled "Sauna bathing is associated with reduced cardiovascular mortality and improves risk prediction in men and women. A prospective cohort study" is a timely and interesting report that clearly presents the impact of sauna bathing frequency and duration on cardiovascular health and mortality in men and women. The authors appear to have accounted for the majority of confounding variables that may be influencing their findings and the results are clear. The major strengths of this study include the prospective nature of the study with a 15 year follow up, the large number of participants, and the clear differences in the results in regard to frequency and duration of sauna bathing on CV mortality and risk prediction.

RE. Thank you for the compliments

More detail should be provided regarding the total physical activity/week. An average of 10-11 hours per week of physical activity and the average of ~2300 met hours/year of are both quite high. Unfortunately a sedentary group that performed frequent sauna bathing was not included to see if sauna bathing, independent of a physically active lifestyle, is protective. The subgroup analysis presented in figure 4 is limited as only 2 groups for physical activity are defined. Based on previous reports from this group, it is surprising that a more thorough analysis with regards to physical activity was not conducted in the current study.

RESPONSE: Thank you for these comments. Ascertainment of physical activity was based on the most common leisure-time physical activities of middle-aged Finnish men. This has now been described in detail in the Methods section. Page 5, Lines 124-130: “The total and energy expenditure of physical activity was assessed from a validated 12-month leisure-time physical activity questionnaire.[24, 25] This detailed quantitative questionnaire deals with the most common leisure-time physical activities of middle-aged Finnish men. For the type of physical activity performed, participants were asked to document the frequency (number of sessions per month), average duration (hours and minutes per session) and intensity.[26] Energy expenditure was measured for each physical activity by multiplying the metabolic index of activity (in metabolic equivalent*hour/week) by body weight in kilograms.”
These variables were skewed and have now been appropriately reported as medians and interquartile ranges as shown in Table 1. We have conducted further subgroup analyses by tertiles of total physical activity/week and energy expenditure of physical activity (Figure 5). Given the exposure categories and the relatively low event rate for cardiovascular deaths (N=181), this precluded detailed assessment of effect modification by relevant clinical characteristics on the associations.

The data presented in Figure 4 is not the clearest in terms of interpretation. Based on the authors interpretation only history of diabetes had a significant impact on modifying the impact of sauna frequency on CVD mortality. However, with regards to sauna duration, it appears that many of the subgroupings had a large impact on the HRs. For instance, body mass, total cholesterol, LDL-C, HDL-C, PA, diabetes, and smoking status all modified the HR such that HR neared 1.

RESPONSE. Thank you for comments. To provide further clarity as requested by Reviewer 1, we have constructed two graphs for sauna frequency and sauna duration respectively (Figures 4 and 5). To test for effect modification by relevant clinical characteristics on the associations, we used formal tests of interaction. Our findings showed that a history of diabetes modified the association between sauna frequency and CVD mortality, evidenced by a p-value for interaction of 0.021. For the association between sauna duration and CVD mortality, there was no statistically significant evidence of effect modification by any of the characteristics evaluated, evidenced by p-values of > 0.10. We agree that there was some impact on the HRs; however, these need to be interpreted with caution as with all subgroup analyses, given the multiple statistical tests for interaction conducted and the low event rates in some of the groups.

Page 10, Lines 278-282: “Except for evidence of effect modification by diabetes status for the association between sauna frequency and CVD mortality, the associations were not modified significantly by levels or categories of several clinically relevant characteristics including gender. However, findings from the subgroup analyses should be interpreted with caution given the multiple statistical tests of interaction and the low event rates in these subgroups.”

It may be worthwhile to state that socioeconomic status (SES) was accounted for in the abstract. For non-European readers the fact that use of sauna bath is not related to SES is surprising.

RESPONSE: Thank you for this suggestion. We have now included in the abstract that socioeconomic status was accounted for.

Page 2, Lines 48-50: “After adjustment for established CVD risk factors, potential confounders including physical activity, socioeconomic status and incident coronary heart disease, the corresponding HRs (95% CIs) were 0.79 (0.57 to 1.09) and 0.34 (0.16 to 0.72), respectively.”
How long before enrollment had the participants been partaking in sauna bathing?

RESPONSE: Thank you for this question. With regard to sauna habits during the previous years before enrollment, the situation is quite similar as with the assessment of other life-style habits such as physical activity, alcohol use, smoking, sleeping etc, in epidemiological studies which commonly rely on the single assessment point of the life-style habits of interest. This information represents well the amount or frequency of the specific activity over the many years (also before the baseline data collection). Thus, collection of sauna frequency data is not different than baseline information on other life-style habits in large and long-term epidemiological studies. We agree that this assessment method is a limitation, as with most epidemiological studies on this nature. It has been included in the limitations section of the revised manuscript. Page 12, Lines 353-356: “We could not account for the longer-term duration and regularity of sauna use prior to the study entry because of the lack of data. However, it is a common way to assess usual life-style activities using baseline questionnaires in long-term epidemiological studies.”

Based on available knowledge, it is well known that most people in Finland commence the habit of sauna bathing at around the age of 16 years and some earlier.

Line 31 page 5: CHD is not defined

RESPONSE: This has now been corrected.

It is interesting that the most frequent sauna bathers (4-7 times per week) also had higher BMI, alcohol intake, and energy intake, all factors that have independently been associated with greater CV risk and mortality. This may provide indirect evidence that sauna bathing protects against other known risk factors

RESPONSE: Thank you for this observation and comment. Sauna bathing is not a physically demanding activity without active muscle work and can be quite easily undertaken by almost everybody, even obese people and those with pre-existing stable cardiovascular disease. As evidenced in our previous reports, sauna bathing has a protective effect on vascular and non-vascular conditions and also has beneficial effects on cardiovascular risk factors.

Line 58 page 10: Should read "men and women" not "men and females"

RE: Thank you. This has been corrected.
Reviewer #3: John Taylor

This study provides unique information on the relationship between use of sauna and cardiovascular disease (CVD) mortality in men and women. Indeed, information on sauna habits adds to conventional risk factors and improves prediction of CVD mortality risk. This is an extension of previous work showing frequent sauna is strongly associated with reduced risk of fatal cardiovascular outcomes and all-cause mortality in middle-aged men. The authors used data on over 1600 eligible participants (roughly half women and men). Risk factors and all other characteristics were assessed at study entry between March 1998 and December 2001. Baseline demographics, socioeconomic and living condition, physical activity, diagnosis of chronic diseases and medications, alcohol consumption, dietary energy intake, resting blood pressure, cholesterol and triglycerides, and body mass index were obtained at baseline. All CVD deaths occurring by end of 2015 were documented with no losses to follow-up. Hazard ratios for CVD mortality were calculated via Cox proportional hazard models. Subjects were classified into groups on the basis of frequency of sauna use. Hazard ratios of the associations of frequency and duration of sauna bathing with CVD mortality were adjusted via several models accounting for age, gender, BMI, smoking, systolic blood pressure, low-density cholesterol, alcohol use, previous myocardial infarction, type 2 diabetes, physical activity per week, socioeconomic status, and incident CHD events. Two CVD mortality risk prediction models were fitted: one model based on traditional risk factors and one with risk factors plus frequency of sauna bathing.

The authors found that those with frequency of sauna bathing 4-7 sessions per week had higher BMI, alcohol and energy intake, compared to those with one sauna session per week, however during a median follow-up of 15 years, cumulative hazard curves demonstrated the lowest risk of CVD mortality among participants in this group. Hence, it is not surprising that adjustment for established risk factors minimally attenuated the Hrs. In analysis adjusted for CVD risks, there was an approximate inverse linear association between duration of sauna and CVD mortality risk. These findings strongly suggest higher frequency and duration of sauna relates to lower risk of CVD mortality in both females and males and that frequency of sauna bathing improves the prediction of 10-year CVD mortality risk beyond established cardiovascular risk factors.

RE: Thank you very much for the encouraging comments.
Reviewer #4: Burkhard Weisser

Well designed study with interesting results

RESPONSE: We appreciate the compliments.

Comments:

p4: "representative": please specify if the participants were representative for an elderly Finnish population or for sauna users etc.

RE: The sample was representative of middle-aged to elderly men and women who use saunas. This has now been specified in the discussion. Page 12, Lines 333-335: “This representative sample of middle-aged to elderly men and women who use saunas, makes it possible to generalize the observed results in Northern European populations; however, prospective studies should be conducted in populations who are not accustomed to regular sauna bathing.”

p4 line 6-9: randomly selected: which was your method of selection? Since there is no random assignment to a group, this is a little bit difficult to understand 1688 elderly participants: " no losses to follow-up" .....? Although not impossible, this is very surprising...

RESPONSE: Participants were randomly chosen from a population register to avoid selection bias. Indeed, there was no loss to follow-up as we have all data on outcomes during follow-up. All participants (just like every individual in Finland) have personal identity codes which are annually matched through computerized linkage with registries for hospitalizations, discharges, and deaths. Annual follow-up for outcomes is also done automatically using the personal identifiers. Registries are also regularly linked with the Central Population Register to ensure that the personal identity codes are correct. This is a unique strength of Finnish studies.

Page 5, Lines 143-147: “All participants (just like every individual in Finland) have personal identity codes which are annually matched through computerized linkage with registries for hospitalizations, discharges, and deaths. Annual follow-up for outcomes is also done automatically using the personal identifiers. Registries are also regularly linked with the Central Population Register to ensure that the personal identity codes are correct.”

Discussion:

I mostly agree with your well written discussion and your conclusion. However, you should consider the possibility that the baseline health status is influencing the frequency of sauna visits
and not only the other way around. The concept that the number of sauna visits is a marker of cardiovascular risk is very convincingly explained, but a causal relation cannot be established by the data of this study. Therefore, a recommendation to increase the number of sauna baths per week to reduce the cardiovascular events is very speculative.

RESPONSE: Indeed, we agree that the baseline health status could be influencing the frequency of sauna visits – reverse causation. We attempted to minimize this by accounting for prevalent clinical conditions and also excluding the first five years of follow-up. We have also emphasized in our discussion that baseline health status may have some effects on sauna habits. We have toned down our recommendations.

Page 12, Lines 337-338: “Our findings were robust to the exclusion of the first five years of follow-up, minimizing the possibility of reverse causation bias as the explanation for our findings.”

Page 13, Lines 384-386: “Our results extend previous evidence that sauna bathing may have cardiovascular benefits; however, further studies are still needed to confirm our findings in different populations as well as also assess the associations of sauna bathing habits with cause-specific cardiovascular events.”

In addition, blood pressure reduction by sauna bathing is one of the mechanisms discussed for the reduction of cardiovascular risk. However, in the present study there was no difference in BP between the groups.

RESPONSE: These results only show baseline BP levels between the groups in a cross-sectional analysis. These cross-sectional results do not imply sauna bathing is associated with blood pressure changes in the future. We have however shown in a previous study that the risk of incident hypertension is lower during the long-term study among those who use sauna regularly (over 4 times per week), compared to those who use it only one time per week.

Last Point: It should be stated as a limitation of the study that there was no control group without sauna use.

RESPONSE: This has been indicated in the limitations section.

Pages 12-13, Lines 356-362: “Secondly, we were unable to assess the associations between sauna bathing and CVD mortality risk when comparing people who used sauna with people who did not use sauna at all (control group). Indeed, majority of Finnish people are accustomed to having a sauna bath regularly at least once per week, as it is traditionally part of Finnish
The associations were unchanged in a subsidiary analysis which employed a combination of people who did not use sauna baths and those who had a single sauna session per week as a reference comparison.”

Reviewer #5: Oliver Gibson

The Manuscript Number: BMED-D-18-00870 entitled Sauna bathing is associated with reduced cardiovascular mortality and improves risk prediction in men and women. A prospective cohort study provides insight into the benefits of sauna bathing as a lifestyle intervention to attenuate mortality in males and females. The inclusion of a combined analysis interacting sauna use with typical CV risk factors provides some novelty beyond the previous work of the group. The manuscript is well written, and the methods and analysis are clearly outlined. I believe that the paper is incremental in the contribution to knowledge in this area and a greater advancement could be made by more explicating dichotomising the cohort into males and females, and by age. In addition to this further analysis, whilst I appreciate the intention to group usage of Sauna by 1, 2-3, and 4-7 times per week to mirror previous work, I think this is a limitation of the analysis, particularly as the group are proposing dose responses. To me it would be more logical to divide the Sauna use into 1, 2-3, 4-5, and 6-7, thus creating more clearly identifiable boundaries for an upper limit of use.

RESPONSE: Thank you for your generous comments. We initially conducted a subgroup analyses by several relevant factors including age and sex. This was reported in our initial Figure 4. Tables 2 and 3 have now been extended to incorporate gender specific estimates. Given the small sample size (number of participants) of the 4-7 sauna frequency category as well as its low event rate (n=8, frequency of 4-7 times per week), further breakdown of this category is not possible.

Below are some more specific comments as per each section –

Abstract

Provide some additional data relating to the dose response and in the latter parts of the abstract include identified target doses of sauna use to attenuate the CVD related events/mortality.

RESPONSE: We have included additional analysis which involved assessing the dose-response relationship between sauna bathing frequency and CVD mortality, using restricted cubic splines. We have now reported data on the dose-response relationship.
Page 2, Line 45: “The risk of CVD mortality decreased linearly with increasing sauna sessions per week with no threshold effect.”

The conclusion eludes to sex differences, yet I am not convinced that the analysis fully explores this. Could separate HI be calculated based upon different doses of Sauna use in males and females and these subsequently calculated.

RESPONSE: As suggested, we have now included detailed gender specific estimates in Tables 2 and 3.

Background
A clear, well cited overview of the area that provides appropriate context.

RESPONSE: Thank you.

Methods
Well written, however the following additions (alterations) could (should) be made
- How were participants recruited?
- State that the 10-20% relates to relative humidity
- State typical sauna duration
- State sauna floor temperature
- State extent of humidity change with water throwing
- Describe blood collection technique
- Consider above point relating to groupings for sauna exposure number

RESPONSE: We have included the above suggestions in the Methods section.

Page 4, Lines 94-99: “We employed the Kuopio Ischaemic Heart Disease (KIHD) study, which is a population-based prospective cohort study designed to investigate sauna bathing habits and other risk factors for CVD.[19, 20] The KIHD study was initially based on a cohort of men aged 42-61 years who were living in Kuopio and the surrounding rural communities in the east of Finland. In the 11-year follow-up visit of the first cohort, women were invited to join this study.”
In this cohort which is being utilized for this analysis, participants (n=2358) comprised a randomly selected sample of 1351 women and 1007 men aged 53.4 to 73.8 years.”

Lines 109-115: “In a traditional Finnish sauna, there is dry air with a relative humidity of about 10-20%. It is possible to increase humidity temporarily by throwing water on the hot rocks of the sauna heater, although it usually remains below 20%. The recommended temperature for sauna is from 80°C to 100°C at the level of the bather’s head, but the temperature is much lower at the floor-level (about 30°C) which keeps ventilation of sauna room efficient and sauna condition comfortable for sauna bathers.[5] The duration of stay in the sauna room depends on the comfort and temperature of the sauna bather, but it usually ranges from 5-20 minutes, although the sessions could be longer depending on the individual.[22]”

Results

It is interesting that more frequent Sauna use is related to higher BMI, alcohol intake and energy intake. Is it the case that access to Sauna, and/or use is limited to only a specific cohort? i.e. wealthy? Does this impact upon their ability to seek medical care or other influences on health more potent than Sauna?

RESPONSE: Our findings are based on a North European population and therefore cannot be generalized to other populations, as we have stated in our limitations section. In Finland, sauna is easily accessible independently of socioeconomic and educational backgrounds, and it is unlikely that these factors may explain the observed findings on sauna and fatal CVD events in this population. Socioeconomic status did not vary between the lowest and the highest sauna frequency group and we also accounted for this in our analysis.

Page 13, Lines 362-364: “In Finland, sauna is easily accessible independently of socioeconomic and educational backgrounds, and it is unlikely that these factors may explain the observed findings on sauna and fatal CVD events in this population; indeed, SES did not vary between the lowest and the highest sauna frequency group.”

Other influences on health more potent than sauna is physical activity, which is well established to have plentiful health benefits. Indeed, our baseline analysis showed that physical activity varied significantly between sauna frequency groups – participants who had 4-7 sauna baths per week were more physically active compared to those who had only one sauna bath per week. However, our analysis showed that the beneficial effect of sauna on mortality was independent of physical activity and also not modified by physical activity. As described in detail on Page 13, Lines 364-377, it is highly unlikely that physical activity accounted for the observed findings. We have also shown in previous reports that a combination of regular physical fitness and sauna
baths is associated with a substantial reduction in the risk of fatal cardiovascular and all-cause mortality events compared with each modality alone.

Our multivariable analyses were planned so that all important and potential confounders were taken into account. Socio-economic background of wealth does not explain sauna use and accessibility of medical care system is not so significantly related to wealth status in Finland. It is not likely that sauna users seek medical care easier than non-users or are familiar with other health influences, which might explain the observed associations. Our health care system is quite equal for everyone. Sauna use is not usually related here in other wealth and social background factors. More discussion on our local life-style, including sauna other health habits, and health care system can be added in the revised manuscript if otherwise appropriate.

Revised hazard ratios should be presented in text following the adjustment for age and gender. Here is where I believe it would be relevant to explore the benefits in four groups, younger males, younger females, older males, older females.

RESPONSE: The event rate in our sample was relatively low. We did not have adequate power to further categorize gender into age groups. Statistically, we would not be able to generate estimates on further breakdown.

Discussion

As outlined above, you have made comments relating to males and females, but not provided clear differentiating data/results between them.

RESPONSE: We have expanded on Tables 2 and 3 and reported gender estimates in addition to the overall estimates.

In the second paragraph, provide some physiological data that characterizes the acute responses to Sauna use, and then the alterations in key dependent variables described which change with repeated Sauna exposures.

RESPONSE: Thank you for the suggestions. We have now added data on the effects of acute sauna exposure followed by data on effects of repeated sauna exposure.

Page 10, Lines 284-293: “Several mechanisms can be postulated to underpin the protective effects of sauna bathing on cardiovascular mortality. Dry and hot sauna baths have been shown
Sauna bathing causes an increase in heart rate which is a reaction to the body heat load. Heart rate may be elevated up to 120-150 beats per minute during sauna bathing, corresponding to low to moderate intensity physical exercise training for the circulatory system without active muscle work.[30, 39-41] Acute sauna exposure has been shown to produce blood pressure lowering effects[42], decrease peripheral vascular resistance [42, 43] and arterial stiffness[17, 44] as well as improve arterial compliance[18]. Short-term sauna exposure also activates the sympathetic nervous and, the renin-angiotensin-aldosterone system, and the hypothalamus- pituitary-adrenal hormonal axis and short-term increases in levels of their associated hormones have been reported[45]. Repeated sauna exposure improves endothelial function, suggesting a beneficial role of thermal therapy on vascular function.[16-18, 46]”

Given 45 min is the optimal total duration, across 4 sessions, does 4 x 11 min of exposure need to be the recommendation? Can the 45 min be divided into uneven exposures, and if so, to what extent? i.e. 1 x 25 min + 3 x ~6.5 min?

RESPONSE: Thank you raising up these practical questions with regard to a single sauna session duration. However, our data was based on total weekly sessions and duration and therefore we are unable to make any definite recommendations. In this study, we had no data available to show if more frequent shorter sauna sessions or sauna sessions with various durations during the week would be similarly related to lower CVD mortality. However, based on historical data, a typical sauna session usually ranges from 5-20 minutes, although longer sauna bathing sessions may be used depending on the individual.

Page 11, Lines 312-317: “The data suggests that increasing the frequency of sauna sessions per week is associated with a decrease in risk of fatal CVD events in a linear dose-response manner. Our data was based on total weekly duration of sauna sessions and therefore we are unable to make any comments regarding the minimum duration of a single session that may confer benefits. However, based on historical data, a typical sauna session usually ranges from 5-20 minutes,[30] although longer sauna bathing sessions may be used depending on the individual.[22]”

Please elaborate on the key point at the foot of page 10. How impactful is Sauna use likely to be on those undertaking regular exercise training i.e. meeting recommended guidelines? Is it such that you are seeing a protective effect because (as described in the results) a gluttonous, inactive group are being assessed vs a healthy active cohort.
RESPONSE: We do not have any data to show the impact of sauna on those meeting recommended exercise training guidelines and therefore we are unable to speculate. However, our previous studies have shown that participants with low fitness levels have a reduced risk of mortality when combined with sauna use. Mortality risk is further reduced in those with very high fitness levels combined with regular use of sauna. We have detailed this in the discussion.

Page 13: Lines 366-378: “We have shown that even participants with low fitness levels have a reduced risk of mortality when combined with frequent (3-7 sessions/week) or infrequent (≤ 2 sessions/week) sauna use. However, mortality risk is substantially reduced in those with very high fitness levels combined with frequent use of sauna. Other studies have also reported similar findings. Iwase and colleagues demonstrated enhance metabolism in participants when isotonic exercise was performed during sauna exposure.[59]. On the effects of sauna bathing on athletes, Ridge and Pyke demonstrated an augmentation in acute physiological responses when sauna exposure followed exercise.[60] In another study in which six male distance runners completed three weeks of post-training sauna bathing, study participants experienced an enhancement in endurance running performance.[61] The overall findings show that physical activity or fitness and sauna bathing each have independent effects on vascular disease,[57, 58] which suggests that the beneficial effects of sauna bathing on CVD mortality is not due to physical activity or exercise.”

Sauna access may be easy in Finland, but this is not true of much of the world.

RESPONSE: Indeed, sauna use is easy in Finland and other Scandinavian countries. However, this trend is changing as its use is becoming increasingly popular in many other continents such as the Americas and the Asian region. This is evidenced by the increasing number of published reports on sauna use from these regions.

Please expand on the benefits of Sauna in conjunction with, and its interaction with regular exercise (consider endurance and resistance)

RESPONSE: Thank you for this suggestion. We have expanded on this and also added appropriate references.

Page 13: Lines 366-378: “We have shown that even participants with low fitness levels have a reduced risk of mortality when combined with frequent (3-7 sessions/week) or infrequent (≤ 2 sessions/week) sauna use. However, mortality risk is substantially reduced in those with very high fitness levels combined with frequent use of sauna. Other studies have also reported similar findings. Iwase and colleagues demonstrated enhance metabolism in participants when isotonic
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Further Editorial Comments

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Declarations

- Ethics approval and consent to participate
- Consent to publish
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions
- Acknowledgements

RESPONSE: We have completed all sections of the Declarations according to journal submission guidelines.