Author’s response to reviews

Title: Cardiovascular Health and the Modifiable Burden of Incident Myocardial Infarction. The Tromso Study

Authors:

Tom Wilsgaard (tom.wilsgaard@uit.no)
Laura R Loehr (lloehr@email.unc.edu)
Ellisiv B Mathiesen (ellisiv.mathiesen@uit.no)
Maja-Lisa Løchen (maja-lisa.lochen@uit.no)
Kaare H Bønaa (kaare.harald.bonaa@ntnu.no)
Inger Njolstad (inger.njolstad@uit.no)
Gerardo Heiss (gerardo_heiss@unc.edu)

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Author’s response to reviews: see over
Dear Editor-in-Chief

Thank you very much in deed, for allowing us to make improvements to our manuscript entitled “Cardiovascular health and the modifiable burden of incident myocardial infarction. The Tromsø Study”. Based on the comments from the reviewers we have made a major revision of our manuscript. Please find enclosed the revised version of our manuscript. The details of our response to the comments from the reviewers are below.

Yours sincerely,

Tom Wilsgaard
Response to the reviewers’ report

Reviewer: Joshua Willey

Major compulsory:

-the authors aim to describe the population impact of life’s simple 7 from the AHA on MI risk. The topic is well known from other cohorts and the benefits in this one would be the longitudinal assessment of the comprehensive measures using time varying covariates.

-please comment on why the GIF was used as opposed to population attributable risk which may be more familiar to many in the audience. Also could the “clinical interpretability” of the time varying covariate method be included versus a single measure? Did the single measure explain the outcome better than the time-varying measure?

Answer: Thank you for this comment. We agree that we could have explained in more detail why we used the GIF. We have added the following comments: “To our knowledge, no study has yet estimated the attributable fraction (AF) of ideal health metrics, i.e. the proportional reduction in disease given complete elimination of an exposure [7]. Moreover, given that complete elimination, as assumed in calculation of the AF, is not realistic for many exposures and that elimination of high risk factor levels from society is unlikely at this stage of prevention science [8], a more realistic and meaningful estimation of the impact of risk factor reduction on disease incidence is the generalized impact fraction (GIF), also known as the potential impact fraction or the generalized AF [9, 10]. It estimates the proportional reduction in disease incidence given a graded reduction in the prevalence of a risk factor or given a graded increase in the number of ideal health metrics”. Please see lines 66-74.

In cohort studies with long follow-up bias might be introduced due to attrition or when the association between a baseline value of a risk factor and event end-point differs from their time-varying association. Our HR estimates, and consequently the GIF’s perform slightly “better” when we include repeated measures of the health metrics compared to using the single baseline measures only. For example, the age adjusted HR’s presented in Table 3 comparing participants in metric score group (0,1) with the ideal score groups >= 4 decreased from 4.40 to 3.93 in men and 6.34 to 5.66 when using the baseline measures of the metrics.

-is the AHA index a truly linear scale? Could this be tested?

Answer: We agree with the reviewer that the AHA health metric score may not be on a linear or ordinal scale. The association between the metric score and MI is assessed in table 2 in the manuscript and a visual inspection indicates that the trend in the log of the HR’s agrees with a linear decreasing trend. The overall test, which includes the metric score as an ordinal variable in the Cox model, is highly significant (p<0.0001 in both men and women). Furthermore, when we include a quadratic term of the ordinal score variable in the Cox model, it is not significant (p=0.36 in men and p=0.39 in women).

-generalizability of their results should be discussed given the unorthodox definition of their AHA index
Answer: We agree with the reviewer that the relatively new AHA index, the health metric, has yet to be studied much. We are not aware of studies that have assessed the generalized impact fraction of the health metrics score in relation to cardiovascular disease. However, the generalizability of our results are strengthened by the fact that Folsom et al. (ref 6) showed a gradient of decreasing incidence of CVD for increasing numbers of ideal health metrics, in line with our results. We have further commented on this, see lines 285-287.

- AF is included in page 7 – what does this stand for. Please introduce all abbreviations throughout the manuscript before using them.

Answer: We appreciate the correction. In the revised version of the manuscript, we have added the abbreviation of the attributable fraction (AF) in the Background section, see line 67.

-The GIF may not be familiar to many in the readership and should be expanded upon

Answer: We agree and have expanded upon the rationale for using the GIF: "Moreover, given that complete elimination, as assumed in calculation of the AF, is not realistic for many exposures and that elimination of high risk factor levels from society is unlikely [8], a more realistic and meaningful estimation of the impact of risk factor reduction on disease incidence is the generalized impact fraction (GIF), also known as the potential impact fraction or the generalized AF [9, 10]. It estimates the proportional reduction in disease incidence given a graded reduction in the prevalence of a risk factor or given a graded increase in the number of ideal health metrics.". See lines 68-74.

-in the results stratified models by age and sex are included but I did not see a mention of a statistical interaction (ie AHA_index*gender, AHA_index*age). Given that the terms may have multiple levels it may well be difficult to detect a statistically significant result. Without that no conclusion can be drawn on differences by age or between men and women.

Answer: This comment is highly relevant. If we use bootstrap, it is indeed possible to compare the GIFs between men and women and between age groups. In a separate set of analyses, we found no interaction between GIF and sex. However, we observed a significant lower GIF in subjects aged 60-69 years compared to those younger than 60 years of age. We have included this information into the manuscript. See lines 171-172, and lines 225-227.

-please put subheadings in the results to help orient the reader as to what the results are pointing to

Answer: We agree with this comment and have put subheadings in the result section of the manuscript.

-the discussion section, particularly on limitations of their manuscript should include more details

Answer: We have included more details in the discussion part of the manuscript. Please see lines 285-287, 289-296, and lines 304-308.
there were a large number analyses included in the supplementary files, it is likely that some of the results were due to chance.

Answer: Both reviewers also commented on the amount of material in the supplementary files. In order to decrease the number of results presented and thus the number of tests, we removed 7 of the files, namely supplemental tables 2-7 and 14. We would like to keep supplemental table 8 – 13 (supplemental files 3 – 8 in the revised manuscript). These tables show the GIFs for the individual health metrics according to age and sex and are included in order to show the age and sex variation in the GIFs for the individual cardiovascular risk factors. Some of the age and sex variation in the individual GIFs may be due to chance. However, we are not performing multiple tests comparing the GIFs.

In order to further reduce the number of tables, we have removed table 3 from the manuscript and instead added this table as a supplemental file 2.

Minor essential

-if it can fit, please include definitions of MI in the abstract

Answer: We have included the following in the abstract: “Incident events of MI were recorded from the date of enrollment in 1994-95 to the end of 2010. Adjudication of hospitalized and out-of hospital events was performed by an independent endpoints committee based on data from hospital and out-of hospital journals, autopsy records and death certificates”.

-please reformat the 3rd sentence in the introduction, it is too long and hard to follow.

Answer: Thanks for pointing this out. We have rephrased the first 5 lines of the background section to: “Trends in the population burden of cardiovascular disease (CVD) and associated lifestyle factors differ between regions of the world [1-4]. Studies of the temporal association of these patterns suggest that changes in lifestyle factors precede the change in CVD outcomes. Effective cardiovascular treatment also contributes to the decline in CVD mortality in Western Europe and USA [2]”. Please see lines 50-54.

Reviewer: Delphine De Smedt
Reviewer's report:
Dear author, thank you for the opportunity to review this very interesting study. This study has a great potential for publication. However, in its current from it is sometimes difficult to follow. Furthermore, the large number of tables and additional files make is sometimes a bit chaotic. The methodology should be described in more detail.

Answer: We agree that there are too many supplemental tables and have removed 7 of them, supplemental tables 2-7 and 14. We would like to keep supplemental table 8 – 13 (supplemental table 2 – 7 in the revised manuscript). These tables show the GIFs for the individual health metrics according to age and sex and are included in order to show the age and sex variation in the GIFs for the individual cardiovascular risk factors. This could be particularly helpful to readers looking for information for a specific age group or age and gender group.
• Major Compulsory Revisions

Methods:
Line 145: explain GIF when used for first time, explain method in more detail

Answer: The methodology and rationale for using the GIF have been described in more detail. Please see lines 68-74.

Line 146: explain AF when used for first time

Answer: Thank you for pointing this out. We have defined AF when first used. Please see lines 67-68.

Line 148: why did you use four groups. Explanation is not clear

Answer: We have added an explanation: “In order to adjust for age, the GIF had to be estimated in age strata. The small number of MI events in the youngest 10 year age groups prevented an estimation of HR for MI for each health metric score level (0 to 6). Consequently, the score was categorized into four groups (≤1, 2, 3, ≥4)”. See lines 158-161.

Statistical methods should be explained in more detail. Explain the method, explain which Tromso surveys were used. Why did you use all the surveys? Why didn’t you use the Tromso 4 as starting point for estimating the HR with a 14 year follow up period?
A rather unusual method (but very interesting) is being used in this paper, hence it is important to explain the hypothesis in more detail, as well as the method used.

Answer: We reviewed our description of the Tromsø study surveys and consider it to be satisfactory, but included this information in the study population section of the manuscript (and not in the statistical method section). We did use Tromsø 4 as starting point, and we have specified which surveys were used. In lines 87-90 we have written “All men and women aged ≥25 years living in the municipality were invited to Tromsø 4 in 1994-95; Tromsø 4 is the baseline population for this study. For Tromsø 4, 27,158 subjects (72% of those invited) attended the study visit.” In lines 95-97 we have written: “Participants that were still under follow-up for MI and attended the later surveys in 2001 (Tromsø 5, n=6455) and/or in 2007-08 (Tromsø 6, n=8221) had their cardiovascular risk factor values updated at the date of their examination”.

We agree with the reviewer that the GIF should be explained in more detail and have already responded to this comment by explaining the rationale for using the GIF, please see lines 68-74. The main hypotheses, or aims, of the paper are listed in the paragraph following the added description of the GIF, see lines 79-82. Furthermore, since we estimated the overall GIF with the case-load weighted sum method we have added a reference to Loehr et al. who explained this method in their appendix (see ref 10).

Results:
There are too many tables and supplemental files. All the information makes it difficult to distinguish the important information from the less important information. The reader loses a bit the focus of the study.
Answer: We agree that the number of supplemental tables is excessive and have removed 7 (supplemental 2-7 and 14). We would like to keep supplemental table 8 – 13 (supplemental files 3 – 8 in the revised manuscript). These tables show the GIFs for the individual health metrics according to age and sex and are included in order to show the age and sex variation in the GIFs for the individual cardiovascular risk factors. Furthermore, we have removed table 3 from the manuscript and instead added this table as a supplemental file 2.

We have also included sub headings in the result section to help orient the reader.

• Minor Essential Revisions

The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

Introduction:
Line 47: please rephrase the first sentence. The meaning of dynamic temporal trends is not clear enough.

Answer: We agree that the first few lines in the Background section may not be clear enough and have rephrased to: “Trends in lifestyles and in population burden of cardiovascular disease (CVD) differ between regions of the world [1-4]. Studies of the temporal association of these patterns suggest that changes in lifestyle factors precede the change in CVD outcomes”.

Line 51-55, this sentence is too long and therefore difficult to read.

Answer: We agree and have split the sentence into 2 sentences. See lines 54-58.

Line 57: explain the PA goal levels and dietary goal levels.

Answer: We have added an explanation of the PA goal level, please see lines 60-61. However, we have chosen not to explain the dietary goal level. The health metric for the diet is not used in the paper. It include 5 aspects of diet to define a healthy dietary score.

Line 66: you might consider to refer to Geoffrey Rose’s prevention paradox.

Answer: Thanks, we have included a reference to G Rose, see ref 12.

Methods:
Line 134 health metric score: Ideal PA is defined as #75 min vigorous PA/week, why did you use 1 hour?

Answer: The question about vigorous PA/week in our questionnaire included 4 answer categories (none, less than 1 hour, 1-2 hours, ≥ 3 hours). We considered our third answer category (1-2 hours) to be the level with the “best” fit with the goal of 75 minutes per week.

Line 145: explain GIF when used for first time, explain method in more detail

Answer: This was a comment also under Major Compulsory Revisions. Please see our response above.
Line 146: explain AF when used for first time

Answer: This was a comment also under Major Compulsory Revisions. Please see our response above.

Line 148: why did you use four groups. Explanation is not clear

Answer: This was a comment also under Major Compulsory Revisions. Please see our response above.

Statistical methods should be explained in more detail.

Answer: This was a comment also under Major Compulsory Revisions. Please see our response above.

Results:
Line 167, what do you mean with last survey? Last survey before event? Please make clear that this is different for every participant included. Also adjust in table 1. (tables should be easy to read without reading the text, so include all necessary information)

Answer: Thank you; our reference to the last examination survey attended before the event was not clear. We have made this clearer in the revised text: “Subjects who attended follow-up examinations in 2001 or 2007-08 and did not experience a MI before the follow-up examination(s) had their cardiovascular health metrics updated. As shown in Table 1, the proportions of subject who had ideal levels of individual cardiovascular health metrics, at last updated value, were lowest in participants with incident MI.” Please see line 185-188 and see footnote to table 1.

Discussion:
Line 232, a reference is needed to justify the case fatality rate

Answer: The 30% case fatality was just a hypothesized scenario. It does not necessarily reflect the true, but unknown case fatality rate in Norway. However, we have now referred to a paper from the Tromsø Study which indicate a case fatality close to 20%. If we use a 20% case fatality and use the fact that 4852 persons died of an MI in 2012 we estimate n=19408 non-fatal MIs. Please see lines 258-59.

Line 237 how did you calculate the 210 NOK?

Answer: After adjusting the case fatality to 20% we have adjusted the number of non-fatal MIs to n=19,408. A GIF of 15% would have resulted in 728 fewer fatal and 2911 fewer non-fatal MIs. The cost of a fatal MI has been estimated to NOK 43,425 and the cost of a non-fatal MI to NOK 114,932 (see line 256-257). Please see our recalculation in line 261

Line 240-243 rephase
Answer: We have rephrased to:”The 7 health metrics considered by the AHA Strategic Planning Task Force [5] are at unfavorable levels at present in Norway [19] and in the US [20]. However, such trends are dynamic [21, 22] and complex in their response to social norms, public education, and market influences [23]”. See lines 266-268.

Please indicate the feasibility of a 30% increase from <4 to #4 ideal health metrics.

Answer: We have added some comments in the discussion section:”In the absence of empirical information it is difficult to determine feasible goals for population-wide reduction in unfavorable levels in several cardiovascular health metrics. We have reported scenarios of 30%, 50%, and 100% decrease in subjects in each score level < 4 to the ideal score group (scores ≥ 4). If the AHA goal for the year 2020 is equivalent to a GIF of 20%, reductions of magnitude between our first two scenarios may have to be met. This goal may be too optimistic, although the recent and rapid population-wide changes in lifestyle related health metrics speak to the dynamic nature of these processes. A 30% reduction could be attainable but may require a downturn of the observed “obesity epidemic”. ” Please see lines 289-296.