Author's response to reviews

Title: Body mass index and incident coronary heart disease in women: a population-based prospective study

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Version: 2 Date: 6 November 2012

Author's response to reviews: see over
To the Editor:

Many thanks for the helpful comments and suggestions of the reviewers of our manuscript which we carefully considered. We took into account these comments when revising our manuscript. Changes in the manuscript are marked in red colour. Please find below the details of our response to these various comments.

Yours,

Dr. Dexter Canoy

Reviewer: Robyn Gallagher

Thank you for the opportunity to review this important and well-written manuscript. The study is very timely as the obesity paradox in relation to cardiovascular disease outcomes is hotly debated. This population level study indicates strongly a dose-effect of BMI on coronary heart disease incidence and deaths. The study focusses entirely on women, and provides an important impetus for population level interventions to address obesity and prevent weight gain given the substantial gains which could be made in women’s mortality.

Minor essential revisions
Only one discrepancy occurs in the paper. While I agree that the effect of BMI occurs across many risk factors including alcohol consumption, it is quite noticeable that non-drinkers have a higher incidence of CHD than non-drinkers, the only risk factor to do so. I think this is worthy of comment. The use of actual numbers in the supplementary figures made this difficult to check against as the reader had to convert the numbers to percentages anyway to make sense (S2). Generally, in the tables the use of raw numbers is not helpful and should be converted or accompanied by percentages (Table 1, Figure S1, Table S2).

Response:
We have now highlight the impact of alcohol consumption and higher BMI on CHD risk in the result (line 222-224) and discussion (line 276-279) sections. We do not think there is any discrepancy in the absolute risks of alcohol drinkers and non-drinkers. Alcohol drinkers in this cohort consumed alcohol only moderately on average (line 167-168). Studies have reported similar pattern of a lower coronary disease risk associated particularly with moderate alcohol consumption as compared to non-drinkers [1], presumably due to improved lipid profile observed with such alcohol consumption [2].

We have modified Table 1 and Table S2 as suggested, to show percentages only. However, for Figure S1, we have retained the details in the figure as these details are relevant and necessary for calculating annual incidence rates.

References

Reviewer: Evan L. Thacker

Major compulsory revisions

"Increasing" vs. "Higher." Throughout the article, please consider revising the language to avoid referring to "increasing" BMI when comparing women who had higher BMI at baseline with women who had lower BMI at baseline. The phrase "increasing BMI" would seem more appropriate for a study evaluating the effects of changes in BMI over time. For comparisons across baseline BMI levels, the phrase "higher BMI" would seem more appropriate. I am concerned that using phrases like "increasing BMI" in this paper may imply that the study shows that individual women who change their BMI over time may experience a change in their coronary heart disease risk. While we certainly hope that may be true, the analyses in this paper do not address that issue. The same idea would apply to the phrases "higher incidence" and "higher mortality" vs. the phrases "increasing incidence" and "increasing mortality.”

Here are a few specific suggestions for revised wording:

- Abstract, opening sentence (line 27): Revise “mortality risk increases with increasing body mass index” to “mortality risk is higher with higher body mass index.”
- Abstract, second sentence of Results (line 39): Revise “incidence ... increased progressively with increasing body mass index” to “incidence ... was progressively higher with higher body mass index.”
- Results, fourth paragraph, first sentence (line 177): Revise “progressive increase in risk with increasing BMI” to “progressively higher risk with higher BMI.”
- Results, fifth paragraph, second sentence (line 192): Revise “increasing incidence of the disease associated with increasing BMI” to “higher incidence of the disease associated with higher BMI.”

Similar wording revisions could be applied throughout the article.

Response:

We have changed the wording as appropriate. ‘Higher’ is a comparative word and is generally more appropriate when one is compared to another (e.g ‘higher than....’). In order to reduce the possibility of any confusion that our exposure variable is baseline BMI rather than change in BMI, we modified some wordings as necessary. We think that it is necessary to use the word ‘increasing’ in specific contexts (e.g. describing shape of the association as shown on a figure or reporting risk estimates for a continuous variable), but we minimised its use to minimise in any confusion regarding the timing of the measurement of BMI vis a vis CHD events. We also made sure that we never refer to any association that might suggest change/increase/decrease in BMI ‘over time’ in relation to CHD incidence and mortality.

Missing data. Some participants were excluded from this analysis because of missing values for BMI (line 116). How many women were excluded for this reason? It is probably only a small percentage of those who were otherwise eligible for this analysis, but seeing the numbers would be reassuring.

Consider stating in the manuscript the total number of women enrolled in the Million Women Study, the number remaining after all baseline exclusions except for missing BMI values, and the number remaining after excluding women with missing BMI values (1,178,939).

Response:

We have added details about the number of women excluded from the analyses (line 120-124).

For adjustment variables, women with missing values were assigned to a separate category (line 129). This method may result in suboptimal adjustment for confounding compared with the method of multiple imputation; however, it may not matter if there is little missing data. How many women had missing values for each adjustment variable? Again, it is probably only a small percentage of women, but seeing the numbers would be reassuring.
Consider stating in the manuscript the number of women with missing values for each adjustment variable — smoking status, alcohol consumption, physical activity level, and socioeconomic status.

Response:
For adjustment variables, we have added the count of women with complete information on the relevant covariates in Table S2. We also added details in the methods (line 158-159) and results (line 228-230) on the risk estimates of women with complete data on all covariates.

Were there any important differences between the adjusted results reported in the article and the unadjusted results, which were not reported?

Response:
No, there were no important differences. We now report the relative risks with minimal adjustment (stratified by region and adjusted for age since the underlying time variable is attained age) as well as with full adjustment for covariates in the results section (line 183-186).

Minor essential revisions
1. Abstract, Methods (line 34): Please state that baseline was 1996-2001.

Response: Baseline recruitment time period is now added in the abstract (line 33).

2. Results, first paragraph (line 153): Please state the baseline age range.

Response: We have now added the baseline age range in the results section (line 165).

3. Results, third paragraph (line 170): The authors state that the relative risk of incident CHD was higher with higher BMI across the range <20 to ≥35 kg/m². However, according to Figure 1, the relative risk in the category <20 kg/m² is a bit higher than the relative risk in the category 20-22.4 kg/m². Please reword the sentence in the Results, first paragraph to resolve this minor discrepancy.

Response: We agree. But the discrepancy regarding the relative risk estimates for BMI of <20 and 20 to 22.4 is minor — their confidence intervals greatly overlap suggesting that their risk estimates minimally differed from each other. However, we have now clarified the statement to indicate that the risk estimates increased progressively from these two lowest BMI categories (line 186-188).

4. Results, fourth paragraph (line 177): The authors state “The incidence for CHD increased with age.” Does this refer to higher CHD incidence for women with higher baseline age, or to increasing incidence of CHD during aging?

Response: We analysed data based on attained age as the underlying time variable. The age-specific analyses in this section therefore refers to age at risk (age of onset of the disease), and could be interpreted as an effect of ageing. We altered the legend for Figure 2 to refer to ‘age’ as ‘attained age’ (page 24).

5. Discussion, second paragraph (line 230): The sentence reads “Thus, our findings provide evidence to the importance of increasing adiposity in the clinical manifestation of CHD.” The meaning of this sentence is unclear, and it should be revised.

Response: This sentence has now been revised as “... increasing adiposity in the occurrence of a coronary event” (line 260-261).
6. **Discussion, fifth paragraph (line 267):** The statement “allowing for competing causes of death generally reduced 20-year rates by about 1%” sounds like it should be placed in the Results section rather than the Discussion section.

   **Response:** We modified the statement (line 300-301) and added relevant statements in the methods (line 159-160) and results (line 230-231) sections as well as in the online supplement Figure S3.

**Discretionary revisions**

1. **Throughout the article, many sentences are very long, with multiple ideas per sentence. Consider breaking sentences apart into shorter sentences for ease of reading.**

   **Response:** We have shortened some sentences where appropriate.

2. **Abstract, Methods (line 35):** Revise “cumulative incidence rates” to “cumulative incidence.” Same revision suggested for Figure 2 and Figure 3 legends.

   **Response:** We deleted the term ‘rates’ from the text in the abstract and in the legend.

3. **Abstract, Results (lines 39-40):** Revise “1 in 11” and “1 in 6” to percentages, and also revise the confidence intervals to percentages.

   **Response:** We prefer to leave this as it is - we use different ways of expressing absolute risks to emphasise key findings and to ensure that risk estimates are communicated meaningfully to the wider public.

4. **Abstract, Results:** Consider giving more numerical results in the Results section of the abstract.

   **Response:** We have added some numerical results in the abstract.

5. **Abstract, Conclusions:** This appears to be a summary only and is redundant with the Results section of the abstract. Can the authors draw any conclusions beyond restating the results? Are there any research, clinical, or public health implications of the findings?

   **Response:** We can only conclude about our findings. The implications of our study are better described in the main text.

6. **Background (line 55):** The authors refer to “this obesity-associated CHD burden” without defining what that burden is. Consider being more specific in the beginning of the background about the degree to which CHD is obesity associated.

   **Response:** We presented results not simply in terms of relative risk but also in terms of absolute risk to provide information on the burden of the disease in this cohort, which we expressed in terms of cumulative incidence.

7. **Methods, paragraph on Calculation, definition and validation of anthropometric variables (lines 95 and 98):** In addition to reporting the correlations of measured and self-reported BMI, consider also reporting the mean difference in kg/m².

   **Response:** We have added the mean difference of BMI based on self-reported and measured data (line 100-102).

8. **Results, fifth paragraph (lines 194-200):** These numerical results are a bit hard to digest from the text. Consider showing them in a figure instead.
Response: The results are all in Figure 3. The numbers quoted here are either for emphasis for some of the findings already shown in Figure 3 as well as providing additional data not shown in this figure.

9. Table 1: Dropping the numbers of participants from the table cells and reporting percentages only would make this table more readable. Consider retaining the numbers of participants in the column headings only. Also, consider breaking the row labeled “Person-years for first CHD event/CHD death (1 000s)” into two rows.

Response: Please see response to the other reviewer (Robyn Gallagher). We have made this change.

10. Figure 1: Consider showing a similar figure with incidence rates, to complement the information about relative risks.

Response: Plotting both incident and death rates of coronary heart disease on the same X axis on the same figure will not be very informative. Because the death rates are very low as compared to incident rates, the cumulative deaths for each BMI category will look flat on the figure which also report on cumulative incidence. Instead, we provided this information in the accompanying numerical data for Figure 1.

11. Figure S1: Consider showing a similar supplemental figure for CHD mortality.

Response: The numbers are too small to calculate reliably CHD mortality rates for each year of follow-up.