Dear Editor,

Hereby we resubmit the manuscript ‘Body mass index and participation in organized mammographic screening: a prospective cohort study’ to BMC Cancer, after additional revisions, as requested by reviewer. Below we make point by point reply to each reviewer’s concern, and explain how we revised the article to address these issues.

We feel strongly that these revisions have improved the manuscript and hope that you will find the comments addressed to your satisfaction, and our article acceptable for publication in your journal.

Reviewer’s comments pertained to lack to address sufficiently earlier review request.

Reviewer: Katherine Reeves

Reviewer’s report:

The authors have not sufficiently addressed the previous comments of the reviewers. Specifically, they have failed to address the importance of utilizing BMI data from roughly 15 years prior to screening invitation, as noted by Reviewer #1, comment #4. This should be thoroughly addressed as a limitation in the manuscript. Additionally, they have not clarified the selection of the cohort as requested by Reviewer #2, comment #1 nor have they appropriately responded to and addressed Reviewer #2, comment #2. Also, they do not seem to appreciate the potential bias associated with their high level of missing data (reviewer #2, comment #4).
Here we address reviewer's comments point-by-point:

Reviewer's report:

Comment 1: The authors have not sufficiently addressed the previous comments of the reviewers. Specifically, they have failed to address the importance of utilizing BMI data from roughly 15 years prior to screening invitation, as noted by Reviewer #1, comment #4. This should be thoroughly addressed as a limitation in the manuscript.

Previous Reviewer # 1. Comment 4. Was BMI from 1993-97 used as a proxy for BMI when a woman was invited in 2008 – a max of 15 years later?

Answer to Comment 1: Actually no. BMI (height and weight) was measured when women were recruited into the Diet, Cancer, and Health Cohort at the baseline, recruitment date, from 1993-97. However, although we say that we use participation data until 2008, this is not entirely correct. We do use data on participation from Copenhagen Mammography Register, and the Register which we use has the data since 1991 until 2008, but we do not use all the data until 2008 in this cohort. The dates until 2008 was used to describe Mammography screening register, but does not reflect that data until 2008 were used. To define participation (or non-participation) in this study, we chose the first invitation date to screening after the cohort baseline date (1993-1997). Given that in the screening program in Copenhagen women are invited every two years, this implies that the longest possible between cohort baseline (1993-1997)/BMI measurement and screening invitation was 2 years, and never 15 years. The outcome was thus dichotomous indicator of non-participation (women who were invited but did not participate) and participation (women who were invited and attended mammographic screening) the average time between measured BMI and screening participation was 1.3 (SD 1.5) years. So although we used Copenhagen Mammography Screening Register in which we have data until 2008, the screening invitations until 1999 were used in this study.

We acknowledge that current description of Methods in the Abstract and the article were confusing, and to make this more clear we made following changes to the manuscript:

We deleted from the Abstract mention of year 2008, as it seems to confuse the reader that this is the end of follow-up for participation, and leave detailed descriptions of cohort, Mammographic Registry and definitions used in this study in Methods section.

We added this sentence on page 6, line 119: ‘As women are invited to screening every two years, maximum time between cohort baseline and screening invitation
was 2 years.’

We change sentence on page 7, line 144: ‘Of 29,875 women in the DCH cohort, 7,507 were invited to Copenhagen mammographic screening between 2001 and 2008.’ To ‘Of 29,875 women in the DCH cohort, 7,507 were invited to Copenhagen mammographic screening.’

We change sentence on page 7, line 147: ‘and mean time from measured BMI to mammographic screening was 1.3 years (SD 1.5).’ to ‘and mean time from measured BMI to mammographic screening invitation was 1.3 years (SD 1.5).’

Comment 2: Additionally, they have not clarified the selection of the cohort as requested by Reviewer #2, comment #1

Previous Reviewer 2, Coment # 1

1. Additional details regarding selection of the study population and overlap between the Copenhagen mammographic screening register is needed. It is unclear if everyone in the DCH population was invited to participate in mammographic screening or not. Also, in the Methods sections the authors note that data from the screening register for 1991 through 2008 were used, but elsewhere in the Results section the time frame given is 2001-2008. Please explain this inconsistency.

Answer 2: To provide even more detail on the merging of DCH cohort with mammographic data from Copenhagen, we added following sentence in the Methods, on page 5, line 83: ‘Of total of 29,875 women in the DCH cohort, 21,154 lived in greater Copenhagen area, and less than a half of these lived in Copenhagen municipality (inner Copenhagen), where mammographic screening was in place since 1991 targeting women aged 50-69 years, and thus providing overlap with DCH cohort women, who were recruited between 1993 and 1999, when they were aged 50-65 years.’

We have furthermore added to the Results section on page 7, line 144, added more details about the steps in selection of the cohort, and added that ‘21,154 lived in greater Copenhagen area’, after ‘Of 29,875 women in the DCH cohort,’ and before ‘and of these, 7,507 who lived in Copenhagen municipality and fulfilled criteria, were invited to Copenhagen municipality mammographic screening.’

The 2001 was typing mistake which was corrected earlier, 2001 was changed to 1991.

Comment 3: nor have they appropriately responded to and addressed Reviewer #2, comment #2.

Reviver 2, Coment # 2

2. Was there a time frame following the invitation to mammography during which a mammogram had to be obtained to count as participation? In other words, would a mammogram received 5 years after the invitation have been counted as “participation”? I would argue that it should not, and that a time frame of 1-2 years following the invitation should be used to determine participation.
Answer 3: We agree with the reviewer that this question was not addressed properly before, and we have now explained in more detail our design as answer to Comment 1. We agree with reviewer that invitation after max 2 years after BMI measurement is most appropriate, and this is exactly what has been done in this study, but was rather poorly described in original version, leading to Comment 1 and 3. See our answer to Comment 1 where we elaborate more on our design, and document that we added more detail to the manuscript to explain this. In brief, we have in our study had BMI measurement at cohort baseline (1993-97), and then used 1st invitation to screening after cohort baseline, which is, mean time 1.3 years after baseline, since Copenhagen mammography program is biannual, and thus women are invited every two years, meaning that maximum time between baseline and invitation to screening can be 2 years.

See answer to Comment 1 for specific changes in manuscript.

Comment 4: Also, they do not seem to appreciate the potential bias associated with their high level of missing data (reviewer #2, comment #4)

Previous Reviwer 2, Coment # 4

4. The number of observations dropped due to missing information is of great concern. The authors note that one-third of the eligible population was excluded due to missing information on covariates. In the Discussion they note that the excluded women did not substantially differ from the included, but these results need to be described in the Results section. Also, the analyses described in the Discussion section note comparisons on the primary exposure and outcome as well as many other covariates. So, it is not clear to me what data they were missing.

Answer: We have added more detail to exclusion criteria at the last revision, as reviewer suggested on page 7, line 147; ‘Excluded 2,373 women did not differ from participating 5,134 women with respect to screening attendance, screening age, educational level, BMI, and smoking status, but were significantly more likely postmenopausal, parous, ever users of oral contraceptives and hormone replacement therapy, and heavy drinkers (data not shown).’

Indeed, large number of women was excluded due to missing data on covariates, since we wanted to (and consider this a strength of the study) to adjust for a large number of lifestyle variables, morbidities (other diseases at baseline), education, etc. variables, as all of these may explain woman’s choices not to participate in screening, and to exclude possibility of confounding by these.

We do document that excluded women did not differ with respect to BMI, our main exposure of interest, or screening attendance, our outcome, and thus, missingness should not impose major bias to our study.

Furthermore, only few women (n=15) in our cohort had missing values on objectively measured BMI, which we state explicitly now in the manuscript on page 7, line 146: ‘of these only 15 women were excluded due to missing data on BMI.’

To address missing data issue more clearly as a weakness of our study, and how this could affect our results, we added following section in the Discussion, under
Study Weaknesses discussion, on page 14, line 306: ‘Another major limitation was exclusion of 32% (2,373) of the eligible women (5,134) due to missing information on screening date or covariates. However, only 15 women were excluded for missing BMI measurements, and excluded 2,373 women did not differ from participating 5,134 women with respect to screening attendance, screening age, educational level, BMI, and smoking status, but were significantly more likely postmenopausal, parous, ever users of oral contraceptives and HT, and heavy drinkers (data not shown). As excluded women were not different from participating women with respect to BMI, our main exposure of interest, or screening participation, our outcome, missing data were not likely to pose major bias in our results on association between BMI and screening participation. Still, due to the fact that women in the study were more likely parous, heavy drinkers, and users of HT and OC than excluded women, the weakness is that our study sample may not be representative of the excluded women and general population.’

Sincerely,
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