Author's response to reviews

Title: High coffee consumption and different brewing methods in relation to postmenopausal endometrial cancer risk in the Norwegian Women and Cancer Study: a population-based prospective study

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Author's response to reviews: see over
Dear Editor,

Thank you for your e-mail of 2 January 2014 informing us of your decision on our manuscript “High coffee consumption and different brewing methods in relation to postmenopausal endometrial cancer risk in the Norwegian Women and Cancer Study: a population-based prospective study” by Gavrilyuk et al. We are very pleased that the reviewers saw fit to allow us to revise the manuscript according to their suggestions, and enclosed you will find the revised version.

We found the reviewers’ comments to be very constructive, and appreciate the thorough feedback on our work. We would like to thank the editor and reviewers as we believe that their input has improved the quality of the manuscript. Our point-by-point replies (in italics) to the comments can be found below. Corresponding changes in the revised manuscript are highlighted in yellow. We hope that these replies have sufficiently addressed the reviewers’ concerns.

We look forward to receiving your final decision and thank you again for considering this revised version.

On behalf of the authors,

Sincerely,

Oxana Gavrilyuk
MD, PhD candidate
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The Faculty of Health Science
The Arctic University of Norway
Reviewer: Dr. Uzochukwu Aniebu

Reviewer’s comment: Sampling is central to success in cohort studies. An investigator intending to determine the generalizability of this study would be interested in having the following answered:

Authors’ response: We agree with the reviewer’s comment. Indeed sampling is central in cohort studies to establish generalizability. As cited in the title, this study investigates endometrial cancer risk associated with coffee consumption in postmenopausal women. The formulation in the text may not have been clear on that point and has been corrected accordingly.

Reviewer’s comment: 1. A) What method of randomization was done. Were inclusion and exclusion criteria specified prior to or subsequent to randomization.

Authors’ response: In this population-based prospective cohort study, the word randomization refers to the original sampling for the NOWAC Study from the population register. Indeed, this kind of randomization can be done only in a few countries. Therefore, to reply to the reviewer’s comment, the sampling was randomized, but the study on which we report here was not.

Inclusion and exclusion criteria were applied to the already random sample of Norwegian women that make up the NOWAC cohort, and therefore subsequent to randomization. In this case our inclusion criteria were postmenopausal status and information on coffee consumption.

We had hoped that by separating the subheadings “The NOWAC cohort” and “Study sample” we would avoid confusion. As it seems that we were unsuccessful, we have made further efforts to clarify the points we mention above in the Methods (page 6 paragraphs 1 and 2).

Reviewer’s comment: B) What were the authors describing as inclusion in the study in "several waves" and how was selection bias avoided.

Authors’ response: Due to constraints in practical workload, limited financial support, as well as the wish to do methodological sub-studies, the enrollment of women was done in 1991-2006 [reference 23]. The enrollment period has been specified in the text, replacing the imprecise wording “several waves of recruitment” (page 6, paragraph 2).

As mentioned in the beginning of the Methods, selection bias was avoided through the random selection referred to in comment A above, i.e., by using the population register in Norway to randomly invite women in defined age groups to the NOWAC Study. The population register contains information about all women living in Norway, including those with temporary work permission, refugees, etc.

Based on our previous study, we can conclude that the women in the NOWAC Study are representative of the Norwegian female population in the corresponding age groups [reference 24].

Reviewer’s comment: C) How long were the respective waves followed up.

Authors’ response: All women were followed till the end of 2010 (generally in NOWAC Study). This makes the range of follow-up time for our study sample:
First wave (1991): 19 years
Second wave (1996): 14 years
Third wave (2003): 7 years

However, in order to avoid confusion between enrollment into the NOWAC Study and the study sample for the present analysis, we have not included this in the text.

**Reviewer’s comment:** 2. Cups of coffee may contain different quantities of coffee except were prepackaged or specified. Consequently a cup may equate 3-4 cups depending on the consumption tendencies of the individuals. Was an attempt made to account for these differences.

**Authors’ response:** The dietary information was obtained from a semi-quantitative food frequency questionnaire, i.e., for most foods, no questions about portion sizes were asked. The cup size for coffee was derived from two methodological substudies [reference 24-26].

This decision is also supported by recent investigations from the Norwegian Coffee Association [reference 21], which are mentioned in the Discussion. The data from their population-based investigations, carried out every 5 years, confirmed an average coffee consumption of 4-5 cups/day during the recruitment period of the NOWAC (1982-2009). In addition, they used a standard cup size of 2.1 dl in their questionnaires. We agree that using standard portion sizes decreases exposure variation, and might increase misclassification, however, it is a problem we share with most large epidemiological studies. We mention this weakness in the Discussion.

**Reviewer’s comment:** 3) What effort were made to exclude recall bias with respect to coffee drinking habit. Was the any attempt at validation of the respondents baseline claims made during the course of this study.

**Authors’ response:** Information on coffee consumption was collected prior to the diagnosis of endometrial cancer, therefore our analysis is free of any recall bias.

We also mentioned in the text that the food frequency questionnaire was validated by 24-hour recall [reference 25] and a test-retest study [reference 26] and indicated the respective correlation and calibration coefficients. The conclusions of these studies have now been clarified in the text (“…which showed good reproducibility and validity on coffee consumption”, page 8, paragraph 2).

**Reviewer’s comment:** 4) Since this is primarily an epidemiological study, professional statistical editing is recommend.

**Authors’ response:** The statistical analyses have been mainly conducted by T. Braaten, who has also supervised the entirety of analyses. Dr Braaten has a PhD in biostatistics and is a co-author of the manuscript.

**Reviewer: Emilie Friberg**

**Reviewer’s comment:** 1) I miss a number of how many women were invited to participate eg response rate, important since you claim representability.

**Authors’ response:** Further to the reviewer’s suggestion, we have added the response rate to the text (page 6 paragraph 2), and added a clear reference to our previous study, which showed that the women in the NOWAC Study are representative of the Norwegian female population in the corresponding age groups [reference 24].
Reviewer’s comment: 2) In collapsing the categories of coffee it is not evident were the individuals answering 6-10 cups/day in the total coffee questionnaire end up. That is, is that categorized as 4-7 cups/d or more than 8 cups/d?

Authors’ response: We would like to thank the reviewer for pointing out this oversight. Women who responded 6-10 cups/day in the total coffee questionnaire were categorized as ≥8 cups/day in the collapsed categories, and we have added this in the text (page 8 paragraph 1).

Reviewer’s comment: 3) I would like to see some mentioning of diabetes, as risk of diabetes have been found to be reduced by coffee and diabetes is an important risk factor for endometrial cancer. I would also suggest adding the number of individuals included with and without history of diabetes, to the description of characteristics.

Author’s response: We have added some results investigating diabetes as a potential confounding factor of the association between coffee consumption and endometrial cancer risk here.

Prevalence of diabetes according to coffee consumption:

≤1 cup: 0.99%
2-3 cups: 0.82%
4-7 cups: 0.92%
≥8 cups: 0.98%

We also enclose an alternate version of Table 2 (uploaded as an additional material file). If the editor and reviewers consider that these results should be presented in the final version, this alternate version can be used for publication. However, we refer to the Results (page 15), where we point out that in our study, “Nevertheless, when analyses were restricted to non-diabetic women, results were similar to those from the entire study sample.”

Reviewer’s comment: 4) The assessment of coffee cup size is “recent,” could one speculate that it might have been smaller at the time of the questionnaire and thus partly explain the very high consumption in relation to previous findings? An average consumption of more than a liter coffee per day is surprisingly high!

Author’s response: In the Discussion we mention the possibility of changes in consumption during follow-up: “We cannot exclude the possibility that coffee consumption reported at enrollment decreases during follow-up for most participants.” (page 17).

However, we think that it is safe to conclude that the consumption that we report is not overstated. We again refer to the statistics obtained from the population-based studies of the National Coffee Association [reference 21], which showed the average coffee consumption during the period of NOWAC enrollment (1982-2009). It is true that the most recent report from this association showed a decrease in coffee consumption in the last 10 years, but we do not believe that this affects our results. On the contrary, it confirms them, as the women in our analysis are elderly and were active heavy consumers during a period of increased coffee consumption in Norway. Moreover, the lack other beverages containing caffeine at the time of NOWAC enrollment and more recent years decreases the influence of these confounders on the relationship between coffee consumption and endometrial cancer risk, thus making our results even more interesting.
In the text page 17:
“This discrepancy might be explained by the fact that Scandinavians used to drink far more coffee than people in other countries [34, 35]. Recent investigations from the Norwegian Coffee Association showed that in the period 1982-2009, which includes the enrolment period of the NOWAC Study, 90% of Norwegians aged over 40 years had an average coffee consumption of 4-5 cups/day [21]. It is possible that such a long tradition of heavy consumption changed the mechanisms involved in the association between coffee consumption and cancer risk. This hypothesis however, needs further exploration. We cannot exclude the possibility that coffee consumption reported at enrollment decreases during follow-up for most participants.”

In the light of the last comment we want to emphasize that difficulties in the validation of dietary assessment in such big population-based studies are common and well-known limitations. However, we believe that our results are reliable due the well documented and published studies showing generally high validation in the NOWAC Study. We also believe that our manuscript will be very attractive to readers, first of all because we are the first to show no effect of different brewing methods (filtered and boiled) related to the well described inverse association between coffee consumption and endometrial cancer risk. In addition, the difference in the number of cups would be interesting to readers and bring new aspects and inspiration for further investigations, as the study took place in population with a well-known, long and unique tradition of high coffee consumption, which is historically different from other European countries.