Author's response to reviews

Title: The National Women's Health Study: assembly and description of a population-based retrospective reproductive cohort

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The Editor
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Dear Editor

Re: Paper formerly entitled “The National Women's Health Study: methods and description of the Study population” (1895676397297526)

(now entitled: “The National Women’s Health Study: assembly and description of a population-based retrospective reproductive cohort”)

Thank you for your email of 21st April, with the comments of two (and later a third) reviewer on the above paper.

We have now addressed the reviewers’ comments and would now like to submit a revised version of the paper. Revisions in response to the reviewers’ comments are highlighted in red type in the text and tables. Please note that we have changed the title to conform with editorial guidelines.

Our response to the independent reviewers’ comments, are attached.

We look forward to hearing from you in the near future.

Thanking you.

Yours sincerely

Noreen Maconochie
Senior Lecturer in Epidemiology & Statistics
Response to reviewers’ reports
All relevant changes are displayed in red type in the text.

Reviewer 1

We thank Professor Alberman for her comments and are pleased that she sees the importance and usefulness of this study.

Comment, Point 4: The introduction of a probabilistic process using forenames to reduce the likelihood of sampling women aged more than 55 is attractive. Can the authors give us any indication of how successful this was.

Estimated UK population figures for 2001 indicate that around 35% of women aged 18 and over were aged 55 and over (we do not know this proportion among those registered to vote). In a sample of around 60,000 this would have produced an estimated 21,000 women who would have been mailed questionnaires unnecessarily. In our study only 5,499 women reported that they were aged 55 and over (9% of the overall sample, 21% of responders). In such a large survey, this represents significant savings in terms of time, money and effort.

Discretionary Revisions:
1. Include definitions of the terms “miscarriage”; “missed miscarriage”; “blighted ova”; and “termination for medical reasons” (and for non-medical reasons)
   These have been added where these terms first appear:
   Miscarriage: Introduction, page 4
   Missed miscarriage: Footnote 4 to Table 2, page 24
   Blighted ova: Footnote 4 to Table 2, page 24
   Termination for medical reasons: Footnote 5 to Table 2, page 24
   Termination for non-medical reasons: page 8; Footnote 6 to Table 2, page 24

2. Explain the significance of the term “offsetting the log odds of the population risk” when calculating standardised values
   This is a standard statistical method used to calculate “observed to expected” ratios, so we would prefer not to go into more detail. We have, however, slightly changed the ordering of the words, and put “offsetting the log odds of the population risk” in brackets, which we hope makes this sentence a little clearer (page 9).

3. Explain the distinction between a multiple birth and a singleton birth where one twin is technically a miscarriage. Presumably the concern is to use the definitions used by national statistics.
   Professor Alberman is correct. The definitions of multiple birth (and stillbirth) are specific to the analyses we have reported in this paper, comparing these outcomes to general population data, and were chosen to be consistent with the national definitions. We have slightly reworded the text to make this clearer (page 9).
Reviewer 2

It was our aim to make this paper as concise as possible. In so doing, however, we feel that we may have left out details which would lead to misinterpretation of the study design by a reader not familiar with the UK electoral system, legislation regarding registration of births, and with common terminology used in the UK to indicate certain pregnancy outcomes.

We feel that this was the case with the second reviewer. We thank her for highlighting this, and hope that we have now clarified all the points raised in her review:

Is the question posed by the authors new and well defined?
We thank Dr Mendola for agreeing the importance and usefulness of this study in obtaining population-based (rather than clinical) data on reproductive health, which throughout the world is very rarely available.

Are the methods appropriate and well-described and are sufficient details provided to replicate the work?
Dr Mendola refers to non-standard work. We agree with this statement but see this originality as a strength. However, we recognise that important details regarding the method of sampling were not included. We have added text on pages 6 to 10, which address the following comments made by Dr Mendola:

1. Electoral roll used as primary sampling frames: who are missing from the registers? (Page 6)

2. Age restriction method: We have provided a lot more detail about how this was done on pages 6 and 7. We take the point that these women could have been excluded following receipt of a questionnaire, but this would have been highly inefficient and expensive (see response to point 4, Reviewer 1)

3. Exclusion of women who had never attempted pregnancy from Stage 2: The issue of infertility is a complex one. In fact we do not report primary infertility in this paper. However the proportion of women reporting that they had attempted pregnancy but failed to conceive (around 3% in both Stages 1 and 2) is about what we would expect from available data in the UK.

Whilst we agree that many women might have periods of unprotected intercourse without conceiving, it would be extremely hard to quantify how many were actually “at risk” of pregnancy, since this requires detailed information on timing of sexual intercourse in relation to ovulation. The more usual definition of infertility relates to people who have tried to achieve a pregnancy for varying amounts of time (depending on the definition) and have failed to conceive (or to achieve a viable pregnancy, depending on definition). There are further issues related to seeking medical help to conceive, diagnosis and treatment. We have
found that the most standard, reliable and ethical means of identifying people with fertility problems (whether or not they subsequently conceive) is to ask for detailed information from those who have ever tried to get pregnant and/or who have ever conceived. We have slightly reworded the description of who was sent a Stage 2 questionnaire at the bottom of Page 7.

4. Exclusion of women with only non-medical terminations in stage 2. Non-medical terminations (sometimes referred to as terminations or abortions for “social” reasons) are terminations of pregnancy for reasons other than that a fetal defect has been identified or that continuing the pregnancy would put the health of the mother at risk. This term was not defined in the text, which led to a misunderstanding. We have now rectified this (page 8) and hope that it is now clear why we did not approach women who had only ever had one or more such termination.

5. Stage 3: why were only women who had had miscarriages since 1995 sent a Stage 3 questionnaire? The information in the Stage 3 questionnaire related only to the case-control analysis of risk factors for analysis. We felt that recall was likely to be best for recent pregnancies, and picked 1995 as it was only 6 years from date of survey. We have clarified the choice of year by changing the text to read “women who had had a miscarriage recently (since 1995)” (page 8). We agree that the description of the third mailing was too sparse, and have now explained it in much more detail on page 8.

6. Case-control analysis: allowance for lack of independence where women have more than one pregnancy in the analysis. We agree with this comment. In all case-control analyses (not reported in this paper) we have used robust standard errors, and have now clarified this in the text (page 9).

7. Definition of multiple pregnancy being non-standard. Please see response to Reviewer 1’s Discretionary revision 3 above.

Are the data sound and well controlled?

1. Reliability: Where we had both Stage 1 and 2 information for women, we examined the information that was common to both for consistency (Stage 1 contained only a brief reproductive history and brief questions about infertility). As both Dr Mendola (in her comments on age restriction) and we note, reproductive events are well recalled and this was confirmed when we found excellent agreement between the two stages. The main areas of difference were (a) where a woman reported a current pregnancy in Stage 1 but had delivered by Stage 2 and (b) where a woman had not reported a non-medical termination (usually a first pregnancy at a very young age) in Stage 1, but reported it in Stage 2. This latter is understandable, since Stage 1 was a “cold” questionnaire from apparent strangers, but for Stage 2 they had much more detail about who we were,
and may even have rung the Helpline to check, so were thus more likely to trust us with this highly sensitive information.

2. Comparison with national dataset - using married women only: We did not have information on marital status for all pregnancies, only for the most recent pregnancy. We hope that we have now made this clearer on Page 10. However, this was not relevant to the analyses of stillbirth and multiple birth, since the national data consisted of births to both married and unmarried mothers. It was only with age at first birth that data were available only for births to married mothers. We explain in the text why we do not therefore do formal statistical comparisons because the data are not strictly comparable. The data were, however, exactly as we would expect.

*Does the manuscript adhere to the relevant standards for reporting and data deposition?*

1. Ethical approval and research governance. We had formal ethical approval for this study and text has been added on page 7.
2. Clarity of reporting. We cannot find the errors in the numbers of subgroups to which Dr Mendola refers, and we hope that the additional information added, and referred to above points, now makes clear how the sample were selected. We feel that a figure or flow diagram is not now necessary, as we think that Dr Mendola’s comments may have arisen from a misunderstanding of the design, as a consequence of our description being too brief and requiring implicit understanding of the UK electoral system.

*Are the discussion and conclusions well balanced and adequately supported by the data?*

Dr Mendola is very concerned about our statements that we regard these data as representative of the UK population. We think this concern results partly from a lack of detail provided by us on the sampling frame and the sampling method itself. We hope we have addressed these points satisfactorily. We have also addressed the points made about apparent non-standard definitions. But, most importantly, we wish to emphasise the importance of the comparison of our data with appropriate and available national data. This comparison showed good agreement. Thus, far from ignoring external validity, we conducted a detailed and entirely appropriate test. We consider that this exercise provided sound evidence that these data are unbiased with respect to reproductive outcome.

*Do the title and abstract accurately convey what has been found?*

Abstract does not convey complexity of sampling and data presented are not sufficient to say sample representative: We have expanded the abstract to include more detail about the study design (page 2) and hope that this is now clear. Regarding the representativeness of the sample, please see immediately above. We have changed the word “representative” to “unbiased” in the conclusion section of the abstract (page 2).
**Major compulsory revisions**
As mentioned above (Are the discussion and conclusions well balanced and adequately supported…?), we hope that we have now addressed Dr Mendola’s concerns satisfactorily.
Reviewer 3

We thank Professor Regan for her very positive comments. We are glad that she recognises the importance and usefulness of this study. There were no revisions to address.