Author's response to reviews

Title: Secular trends in age at menarche and time to establish regular menstrual cycling in Japanese women born between 1930 and 1985

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Author's response to reviews:

December 21, 2011

Nina Titmus
Rachel Neilan, Executive Editor
BMC-series Journals
BioMed Central Floor 6,
236 Gray's Inn Road, London, WC1X 8HL

Dear Ms Nina Titmus

Re: MS:1861719347538137 “Secular trends in age at menarche and time to establish regular menstrual cycling in Japanese women born between 1930 and 1985: cross-sectional study” by Michie Hosokawa, Setsuko Imazeki, Hideki Mizunuma, Toshiro Kubota and Kunihiko Hayashi

We are most grateful to you and the referees for the helpful comments on the original version of our manuscript. We have taken all these comments into account and submit a revised version of our paper. We have addressed all the comments by referee 1 and referee 2, as indicated on the attached pages, and we hope the explanations and revisions of work are satisfactory.

I'm sorry. I wrote a different address in the cover letter of April 7, 2011 by mistake. We confirm this manuscript is not under consideration elsewhere.

In your email you suggested that we should provide a statement regarding informed consent. I added Methods section on page 4 of revised manuscript
about informed consent. “Nurses were informed of the purpose and procedures of the study in the invitation letter, and women who agreed filled out the self-administered questionnaire with a written consent sheet and replied by mail.”

All the authors have read and approved this revised manuscript. Full-length of this article is 2892 words and length of abstracts is 350 words. Thank you for considering our manuscript.

We hope that the revised version of our paper is now suitable for publication in the BMC Women’s Health and we look forward to hearing from you at your earliest convenience.

Yours sincerely,
Michie Hosokawa.

We are grateful to referee 1 for the critical comments and useful suggestions that have helped us to improve our paper considerably. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of our paper.

Comments by referee 1

Major Compulsory Revisions

Comment #1

I am not aware of much evidence that women with regular cycles have higher estradiol levels than those without irregular cycles? See PMID: 10770172.

Possibly with under nutrition related amenorrhea, but there are other causes of irregular cycles. This is a key tenet to their analyses and should be explicitly discussed and referenced.

Response

Thank you for your advice. According to the study recommended [PMID: 10770172], estradiol showed a significant increase in the regular menstrual cycle group during the first 6 year after menarche. We add discussion on page 10 of the revised manuscript. ”Estradiol showed a significant increase in the regular menstrual cycle group.” and the reference [new reference #24].

In younger generations irregular cycles was obviously increasing in our study. However, we don’t have a data about factors affecting amenorrhea such as nutritional status in their childhood. Therefore, as you suggested, we infer causes of irregular cycles using previous studies in the discussion section.

We added the next sentence to discussion and referenced on page 9 of revised
manuscript. “According to previous studies, a common etiology for amenorrhea is weight loss, related to dieting and a desire for thinness. And an increase in athletic activities, emotional stress related menstrual pattern [new reference #20]. The increasing of the proportion of women who has irregular cycles in our study may be affected by the change of the life style with the times such as nutrition.”

Added reference


Comment #2

Rather than indirectly conjecturing that the distribution of the age at start of ovulatory cycles has widened, the authors could directly calculate age at onset of regular menstrual cycles and explore how this variable and its variance directly changes with birth year.

Response

Thanks for your advice. However, we asked participants time to onset of regular menstrual cycles using five categories: <1 year, 1-2 years, 3-4 years, #5 years, and still irregular. So we can’t know exactly the age at start of regular menstrual cycles as continuous data. We added the next sentence to discussion section on page 9 of the revised manuscript. “We asked participants time to onset of regular cycles using five categories, we could not calculate the exact age at start of regular menstrual cycles.”

(For Your Information)

If we could assume the numerical value of age at start of regular menstrual cycles, the following results could have been obtained. We replaced the category to the numerical value for reference, <1 year was transposed to 0 year, 1-2 years was transposed to 1 year, 3-4 years was transposed to 3 years, #5 years was transposed to 5 years, still irregular was transposed to 10 years. And we calculated the start age of a regular period. As shown table A and table B, the women whose calculated start age was 10 years old or younger increased in the younger generations. And the women whose calculated start age was 22 years old or older were increased in younger generations. It can be said, the distribution of the calculated age at onset of regular menstrual cycles is similar to Figure 2 of the original manuscript, the distribution of the calculated age at onset of regular menstrual cycles has widened.
Table A: Distribution of the calculated age that a regular menstrual cycle started

<table>
<thead>
<tr>
<th>Year of birth (%)</th>
<th>1930’s</th>
<th>1940’s</th>
<th>1950’s</th>
<th>1960’s</th>
<th>1970’s</th>
<th>1980’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-10</td>
<td>0</td>
<td>0.5</td>
<td>0.7</td>
<td>1.3</td>
<td>1.5</td>
<td>2.5</td>
</tr>
<tr>
<td>11-14</td>
<td>35.9</td>
<td>38.5</td>
<td>45.8</td>
<td>45.9</td>
<td>42.5</td>
<td>37.4</td>
</tr>
<tr>
<td>15-17</td>
<td>34</td>
<td>35.6</td>
<td>33</td>
<td>31.4</td>
<td>30.2</td>
<td>32.4</td>
</tr>
<tr>
<td>18-20</td>
<td>30.2</td>
<td>25.4</td>
<td>20.6</td>
<td>21.4</td>
<td>25.8</td>
<td>27.7</td>
</tr>
</tbody>
</table>

Table B: Distribution of the calculated age that a regular menstrual cycle started

<table>
<thead>
<tr>
<th>Year of birth (%)</th>
<th>1930’s</th>
<th>1940’s</th>
<th>1950’s</th>
<th>1960’s</th>
<th>1970’s</th>
<th>1980’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0.5</td>
<td>0.6</td>
<td>1.2</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td>11</td>
<td>1.9</td>
<td>1.9</td>
<td>3.3</td>
<td>5.7</td>
<td>5.7</td>
<td>5.0</td>
</tr>
<tr>
<td>12</td>
<td>8.5</td>
<td>7.5</td>
<td>10.7</td>
<td>11.5</td>
<td>11.3</td>
<td>10.4</td>
</tr>
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<td>13</td>
<td>8.5</td>
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<td>15.1</td>
<td>13.1</td>
<td>13.3</td>
</tr>
<tr>
<td>14</td>
<td>17.0</td>
<td>15.8</td>
<td>15.4</td>
<td>13.6</td>
<td>12.6</td>
<td>8.6</td>
</tr>
<tr>
<td>15</td>
<td>9.4</td>
<td>15.1</td>
<td>14.0</td>
<td>12.8</td>
<td>12.2</td>
<td>14.4</td>
</tr>
<tr>
<td>16</td>
<td>14.2</td>
<td>10.9</td>
<td>9.4</td>
<td>9.5</td>
<td>8.8</td>
<td>9.0</td>
</tr>
<tr>
<td>17</td>
<td>10.4</td>
<td>9.6</td>
<td>9.6</td>
<td>9.2</td>
<td>9.2</td>
<td>9.0</td>
</tr>
<tr>
<td>18</td>
<td>8.5</td>
<td>7.1</td>
<td>6.1</td>
<td>5.5</td>
<td>4.9</td>
<td>4.0</td>
</tr>
<tr>
<td>19</td>
<td>7.6</td>
<td>4.6</td>
<td>4.2</td>
<td>3.6</td>
<td>3.5</td>
<td>1.8</td>
</tr>
<tr>
<td>20</td>
<td>1.9</td>
<td>2.5</td>
<td>1.7</td>
<td>1.6</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>21</td>
<td>0.9</td>
<td>1.0</td>
<td>0.9</td>
<td>2.0</td>
<td>3.4</td>
<td>4.0</td>
</tr>
<tr>
<td>&gt;=22</td>
<td>11.3</td>
<td>10.3</td>
<td>7.7</td>
<td>8.7</td>
<td>12.5</td>
<td>16.6</td>
</tr>
</tbody>
</table>

Minor Essential Revisions

Comment #3

While they present an impressive total sample size (n~48,000), the numbers born
in the 1930s (n=106) and 1980s (n=278) are very small so in effect they study changes between 1940s and 1970s. For comparisons it would be better to select 1970s as the reference decade.

Response

The number of subjects born in 1930's is relatively small. However, the data is very important when looking at the trend of age at menarche among different generations. In addition, the data of 1980's are important data suggesting that a decline of the age at menarche stops. Sample sizes of these generations are small as compared with other generations, but the mean age at menarche of 1930's and 1980's respectively represent typical values of the age at menarche of that generation's women, so that the sample sizes are enough to see the trend.

Comment #4

The associations between age at menarche and cancer risks are linear, so it is unclear why such a rare high risk group needs to be defined by menarche by 10 years and regular cycles within one year.

Response

As was pointed out that the associations between age at menarche and cancer risks are linear. Previous study has stated that early menarche and rapid establishment of cycles (within one year) had an almost fourfold increased risk of breast cancer compared with women with later menarche and longer duration of irregular cycles (8 of reference of original paper). We thought it is important that age at menarche, but also the onset of ovulatory cycles for starting exposure to ovarian hormones. We asked participants time to onset of regular menstrual cycles using five categories, but we couldn’t calculate age at onset of regular menstrual cycles, as we mentioned at Comment #2. So we focused on high-risk group by defining women who experienced menarche by 10 years old and regular cycles within one year.

We added to limitation on page 11 of the revised manuscript.

“We asked participants time to regular cycles using five categories, we couldn’t calculate age at onset of regular cycles. We defined high risk group by women experienced menarche by 10 years old and regular cycles within one year.”

We are grateful to referee 2 for the critical comments and useful suggestions that have helped us to improve our paper considerably. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of our paper.

Comments by referee 2

Comment #1
Is the question posed by the authors well defined? Comments: Yes

Comment #2

More details needed regarding sampling strategies

Response

I added method section on page 4 of revised manuscript as followed: We announced recruitment to the study at conferences of the Japanese Nursing Association and the Japan Menopause Society, by advertisements in newsletters sent to members of the Japanese Nursing Associations, by invitation from the Japan Nurses' Health Study Recruitment Committee. Interested medical institutes or individual nurses requested baseline questionnaire sets from the JNHS coordination center by application postcard, facsimile, e-mail, or telephone. At some nurses' conferences and hospitals, we distributed the baseline questionnaire sets directly to individual nurses.

Comment #3

Are the data sound? Comments: Yes

Comment #4

Does the manuscript adhere to the relevant standards for reporting and data deposition? Comments: to some extents.

Comment #5

Are the discussion and conclusions well balanced and adequately supported by the data? Comments: More discussion is needed, mentioning others study in South Asian Countries.

Response

Thank you for your advice. We add a reference [new reference #5: PMID: 8810202] to the first line of the background on page 3 of the revised manuscript. And we added the first line of discussion and referenced on page 8 of the revised manuscript, thus “Age at menarche has decreased worldwide [1, 2, 3, 4, new reference #5].”

Added reference


Comment #6

Are limitations of the work clearly stated? Comments: To some extents.
Comment #7
Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?  Comments: Yes

Comment #8
Do the title and abstract accurately convey what has been found?
Comments: Title may be reduced in length.

Response
Thank you for the advice. We revise a title based on your advice as follows;

Comment #9
Is the writing acceptable?
Comments: This paper only highlighting the secular trends of menstrual age but more reasons should be reported regarding this event. In the present form, it will not be accepted for this journal but if the author will able to incorporate the above mentioned facts, then this paper is acceptable for publication.

Response
The objective of this study was to describe secular trend of age at menarche, not to determine factors affecting the onset of menarche. Moreover, we did not have information about such factors in early stage of life, except birth weight. Therefore, we add some inference about ‘reason’ in the discussion section (please refer our response to the comment #1 of Referee #1). We added the next sentence to discussion and referenced on page 9 of revised manuscript.
“According to previous studies, a common etiology for amenorrhea is weight loss, related to dieting and a desire for thinness. And an increase in athletic activities, emotional stress related menstrual pattern [new reference #20, PMID: 2695202]. The increasing of the proportion of women who has irregular cycles in our study may be affected by the change of the life style with the times such as nutrition.”

About the birth weight as a potential reason of the secular trend, we will modify a part of discussion about the description of logistic-regression models. Then we show the secular trend of birth weight, that is the only data in potential factors noted concerned. We add the next sentence to discussion on page 8 of the revised manuscript.

“By birth cohort, average birth weights were increasing as follows: 1930’s, 3.16 kg; 1940’s, 2.91 kg; 1950’s, 2.95 kg; 1960’s, 3.01 kg; 1970’s, 3.08 kg; 1980’s, 3.08 (p < .0001). Terry showed negative association between birth weight and
age at menarche [17], the present study did not obtain any data on BMI at age of menarche but on birth weight. To assess associations between birth weight and age at menarche, we used logistic-regression models for earlier age at menarche relative to later age at menarche. The results showed negative slight association between birth weight and age at menarche (data are not shown). This association is similar to the study by Terry [16]. However, the association between birth characteristics and age at menarche has been less consistent [14]. The association between birth characteristics and age at menarche remains to be investigated. However since we did not have information of potential confounders such as nutritional status affecting age at menarche, we could not conclude that only birth weight has influenced earlier menarche.”