

OBSTETRICS & GYNECOLOGY



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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:
obgyn@greenjournal.org.

Date: Mar 05, 2020
To: "Takayuki Tatsumi" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-218

RE: Manuscript Number ONG-20-218

Analyses of age-dependent and seasonal changes of menstrual cycle length and basal body temperature using 6 million cycle data

Dear Dr. Tatsumi:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Mar 26, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is an interesting report that utilizes new digital technology, as maintained by millions of Japanese women in their day-to-day lives, to provide fresh data on the historical question of variation in menstrual cycle length across the reproductive age span, and as a function of the environment. The authors correctly point out that there has not been a meaningful update on menstrual cyclicity, BBT and age for half a century, and that one cannot generalize from one country or ethnic group to another. Therefore, the topic of this paper, and its contemporary approach to data collection, is welcomed.

The main finding - that menstrual cycle length increases in adolescence, declines from the mid-20s through the mid-40s, and rises thereafter - is (as the authors point out) consistent with our understanding of reproductive neuroendocrinology across these ages. I have one major question regarding the data and their interpretation, however: by including "cycles" that are very short (calendar lengths down to 7 days were included) and very long (calendar lengths up to 90 days were included), do the data represent a mix of ovulatory cycles and calendar bleeding intervals that like reflect anovulation? Indeed, on lines 222 and 223, the authors refer to PCOS which "causes defective ovulation, resulting in elongation of menstrual cycle." First, while PCOS may cause "defective" ovulation in some true menstrual cycles, it most frequently causes anovulation. The lengthening of some calendar intervals of bleeding in women with PCOS, and the shortening of bleeding intervals at other times, represents anovulatory bleeding, and probably shouldn't be included at all in a study of menstrual cyclicity. Similarly, women with other causes of anovulation, such as hypothalamic amenorrhea, hyperprolactinemia, etc. may be included in the authors' "menstrual cycle" data base with very short or long bleeding intervals, even though they are not ovulating or having menstrual bleeding. Therefore, I would recommend that the authors repeat the analysis, restricting cycles to a narrower window - perhaps 15 to 45 days - to be more assured that the data reflect variations in menstrual cyclicity as a function of age, climate, etc., rather than an admixture of menstrual cycle bleeding and anovulatory bleeding. Even if the pattern with age remains (which is an empirical question to be answered), it is likely that the variance around the mean will be lower.

Regarding their discussion of BBT and follicular and luteal body temperature, it is likely that the key reason that these women are recording their temperature is as a measure of ovulation, either for pregnancy promotion or prevention. Thus, as the authors write, "the biphasic nature of the menstrual cycle is a useful indicator for women who want to become pregnant." By focusing on mean follicular and luteal temperatures, the author miss the opportunity to present data on the change in temperature from the follicular to luteal phase—the extent to which this is detected among the women who recorded their temperatures, the amount of temperature change associated with bleeding x days later, variation with age and environment, etc.

Finally, regarding the statistical analysis, I have two comments. First, the authors report that menstrual cycle length did

not follow a normal distribution. What was the distribution - what it skewed in one direction or the other? Does it more resemble a normal curve after restricting cycle length to a narrower window like 15 to 45 days? What is the reference for "Box-Cox" transformation and why was this particular transformation used? Second, the authors cite their own previous papers in the methodology section when commenting that generalized estimation equations were used to adjust for confounding factors and for within-person correlations of multiple records. When referring to the references given, it is stated that "we used GEE adjusting for correlations within the same patients, for a binomial family using the logit-link function," but no reference is given for the logit-link function or how it corrects for correlations within patients for a binomial family. The authors should reference the statistical paper that is the basis for this approach to analysis, and provide one or two sentences explaining the method intuitively.

Reviewer #2: The authors present an interesting work on menstrual cycle length using unique technologies such as an app. This is an interesting topic that has not been apparently reproduced since the late 1950's and 1960's. Overall I found this work to be reasonably well written with a clear and cogent hypothesis. While I normally do not believe that clinical questions that have already been answered should be replicated, in this case due to changes in environmental factors I think it is reasonable and the approach appears sound.

Specific comments:

- 1) Lines 84-87: Because your population is so homogeneous what is the generalized applicability of your data world wide? This is a both a strength and weakness of your work.
- 2) Line 91- what is the reproducibility of the data from this app? Has in been validated?
- 3) Line 158: This is awkwardly written, please address
- 4) Line 174- what is the biological explanation of the longest cycle length being at age 23
- 5) Line 200-203 is the most interesting data in your set in an era when climate change is so discussed- please expand on this in your discussion
- 6) The figures are well done and easy to understand

Reviewer #3: This study assesses basal body temperature and cycle length in a large number of Japanese women who entered data on a smart phone app.

Reassessment of the characterization of the menstrual cycle compared to data obtain more than 50 - 80 year ago has value.

This study does add information about gaps in our knowledge on the subject regarding effect of temperature and season, but generally does not add novel or new information.

Limitations include lack of rationale of the importance or biological significance of basal body temperature in the follicular and luteal phase.

Specific limitation includes:

The study does not before any sensitivity analysis such as restriction to only one cycle per person, or assessment of cycle in the same women.

The study is essentially cross sectional so care much be taken regarding verbs like continuous changes over time or age.

The generalizability of the study is low give the homogeneity of the population.

Table 1 and 2 are statistically correct, but lack clinical interpretability

While this is an interesting use of big data, it unfortunately does not add substantially to current understanding of the menstrual cycle.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

While Tables 1, 2, 3 show many statistically significant associations of temp vs age, season, average temp, precipitation or sunshine, the correlations are actually quite weak. That is, they are statistically significant owing to the large sample, but would have wide variability for prediction in an individual case.

Therefore, the figures, which are useful for summarizing the data, show how wide the variability is.

Also, as acknowledged by the Authors, the data missing re: wgt or BMI may have been important covariates that affect body temp.

Also, these data re: months of year are applicable to the Northern Hemisphere and presumably would be reversed in the Southern hemisphere and may be influenced generally by latitude.

Finally, the data show the importance of individual women recording serial data to determine their own profile of temp during menstrual cycle.

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

Line 42: The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstracts conclusion. Précis should be the "hook" for people who scan the Table of Contents to see what to read. It shouldn't include statements like "in this study" or "we found". Just state what you found. Also, please eliminate the statement that "This is novel as it is not relevant for the précis.

In the manuscript, this would be considered a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the data bases you have searched (PubMed, Google Scholar, EMBASE for example) and the search terms used. IF not done, please edit it out of the paper.

Line 46: The objective of the abstract should be a simple "To" statement without background information. Eliminate the background section.

Please add the unit of measure of cycle length in the abstract, and if not present there, in the manuscript and tables as well.

Line 59: Should read "temperature WHICH showed no significant change...."

Line 61 includes causal language (...temperature did not affect....). Here and throughout your paper, this should be replaced with associative language. As an observational trial, you can not demonstrate causation.

Line 63: Instead of "big data" please state something like "data self-entered into a smart phone application".

Line 69: Perhaps "Current understanding of menstrual cycle length and basal body temperature is based on...". Also, "knowledge" should be singular, not plural.

Line 80 Instead of "interesting" perhaps substitute "unknown".

Line 82: "is expected to be so subtle.."

Line 93: Basic functions...ARE freely available...

Line 118: Instead of "kids" please state "greater than 5 children"

Line 127 : One of your reviewers suggests eliminating cycles that could be related to PCOS. I'm not sure how you would

do this in reality so I'm not in favor of you making that change. Perhaps doing a subanalysis of cycles from 45-90 days makes some sense, however, as anovulatory bleeding from what ever cause may be more likely to fall into this time frame and should not really be considered a "menstrual cycle".

Did you collect contraceptive information? This should be added, if not, as many forms of contraception influence cycle length. Without this information, unfortunately, this paper may not be acceptable.

Line 159 Peak in mid-30's. Please add units for age throughout.

Please limit age, Cycle length, BMI to 1 decimal. Taking that data to the 100's place does not really convey any useful clinical information.

Line 176: the value increased rather than "turned upward".

Line 204 as written does not make sense. Do you mean "We found no correlation between climatic factors and cycle length" or may "There was little association between climactic factors and cycle length"?

Line 224 :Instead of "alleviate" perhaps "stabilize" or "Improve"?

Line 231: Perhaps "These findings are in agreement with...".

Lines 247: :fewer" than what? And likewise, line 249 "more" than what?

Line 250: Primacy claim here. Please address as noted above.

Line 264: Not clear what you mean "self controllable"? Perhaps "Self motivated"?

Line 274; again, would change to avoid causal language here.

EDITOR COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

- A. OPT-IN: Yes, please publish my point-by-point response letter.
- B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

5. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A

Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

6. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

7. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.

8. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

11. The commercial name (with the generic name in parentheses) may be used once in the body of the manuscript. Use the generic name at each mention thereafter. Commercial names should not be used in the title, précis, or abstract.

12. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

13. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%).

14. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

15. Figures 1 and 2 may be resubmitted with the revision as-is.

16. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifauth.htm>.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

17. If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

- * A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and
- * A point-by-point response to each of the received comments in this letter.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Mar 26, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.

Response to Editors' and Reviewers' comments

We thank the Editors and Reviewers for their comments. Please find our responses to the comments below:

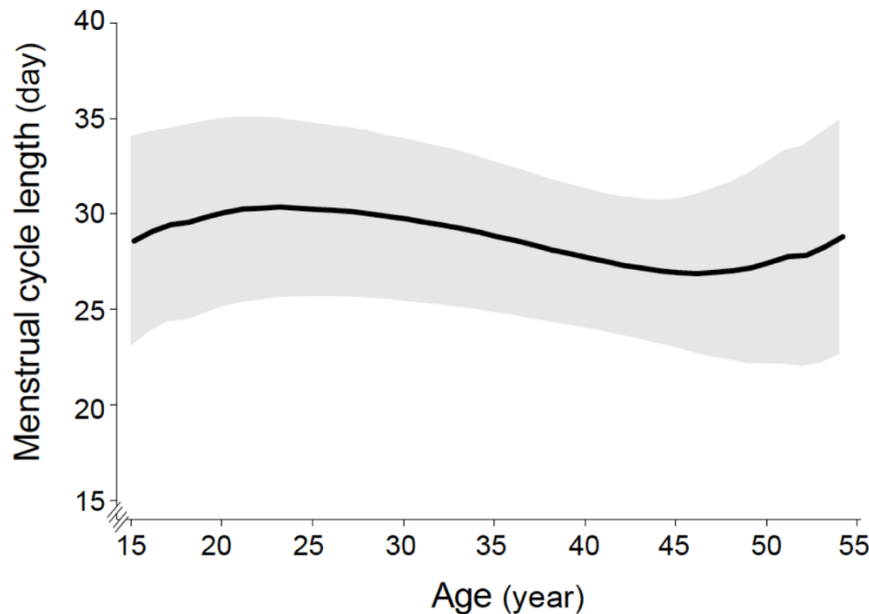
Reviewer #1's comment

This is an interesting report that utilizes new digital technology, as maintained by millions of Japanese women in their day-to-day lives, to provide fresh data on the historical question of variation in menstrual cycle length across the reproductive age span, and as a function of the environment. The authors correctly point out that there has not been a meaningful update on menstrual cyclicity, BBT and age for half a century, and that one cannot generalize from one country or ethnic group to another. Therefore, the topic of this paper, and its contemporary approach to data collection, is welcomed.

Response: We greatly appreciate the reviewer's interest in our study.

Comment 1: *The main finding - that menstrual cycle length increases in adolescence, declines from the mid-20s through the mid-40s, and rises thereafter - is (as the authors point out) consistent with our understanding of reproductive neuroendocrinology across these ages. I have one major question regarding the data and their interpretation, however: by including "cycles" that are very short (calendar lengths down to 7 days were included) and very long (calendar lengths up to 90 days were included), do the data represent a mix of ovulatory cycles and calendar bleeding intervals that like reflect anovulation. Indeed, on lines 222 and 223, the authors refer to PCOS which "causes defective ovulation, resulting in elongation of menstrual cycle." First, while PCOS may cause "defective" ovulation in some true menstrual cycles, it most frequently causes anovulation. The lengthening of some calendar intervals of bleeding in women with PCOS, and the shortening of bleeding intervals at other times, represents anovulatory bleeding, and probably shouldn't be included at all in a study of menstrual cyclicity. Similarly, women with other causes of anovulation, such as hypothalamic amenorrhea, hyperprolactinemia, etc. may be included in the authors' "menstrual cycle" data base with very short or long bleeding intervals, even though they are not ovulating or having menstrual bleeding. Therefore, I would recommend that the authors repeat the analysis, restricting cycles to a narrower window - perhaps 15 to 45 days - to be more assured that the data reflect variations in menstrual cyclicity as a function of age, climate, etc., rather than an admixture of menstrual cycle bleeding and anovulatory bleeding. Even if the pattern with age remains (which is an empirical question to be answered), it is likely that the variance around the mean will be lower.*

Response: As pointed out by the reviewer, the menstrual cycle is generally considered to be about 15–45 days. According to the reviewer’s suggestion, we performed a sub-analysis focusing on cycles of 15–45 days. Supplementary Figure 5A is shown below.



In the upper diagram, the horizontal axis indicates age (years) and the vertical axis indicates menstrual cycle length (days). The analysis limited to cycles of 15–45 days included 5,392,111 cycles, corresponding to about 90% of all cycles (7–90 days). The longest mean menstrual cycle length (30.36 days) was observed at age 23 years. The curve of cycle length showed relatively less variance, as predicted by the reviewer, but the chronological change in mean values was comparable to those of the previous analysis using the data for 7–90 days.

We also conducted additional analysis using GEE (corresponding to Table 1) for data restricted to cycles of 15–45 days (Supplemental Table 3).

Characteristic	Menstrual cycle length (n = 798,589)		Menstrual cycle length restricted to 15-45 days (n = 768,563)	
	95% CI [†]	p value [*]	95% CI [†]	p value [*]
Age (year)				
≤19	Reference		Reference	
20–24	.327 – .682	<.001	.422 – .768	<.001
25–29	.272 – .621	<.001	.389 – .729	<.001
30–34	-.325 – .021	.085	-.200 – .137	.712
35–39	-1.32 – -.970	<.001	-1.22 – -.882	<.001
40–44	-2.37 – -2.02	<.001	-2.32 – -1.99	<.001
45–49	-2.51 – -2.14	<.001	-2.75 – -2.39	<.001
≥50	-1.23 – -.604	<.001	-2.05 – -1.42	<.001

Season				
Spring	.008 – .054	.009	-.044 – .003	.086
Summer	-.063 – -.016	.001	-.118 – -.070	<.001
Autumn	-.029 – .019	.698	-.063 – .014	.002
Year				
2016	Reference		Reference	
2017	-.086 – -.039	<.001	-.072 – -.026	<.001

The total number of cycles of 15–45 days analyzed was 768,563, corresponding to about 95% of the number of cycles of 7–90 days analyzed. The results of the additional analysis were comparable to those of the previous analysis using the data for 7–90 days.

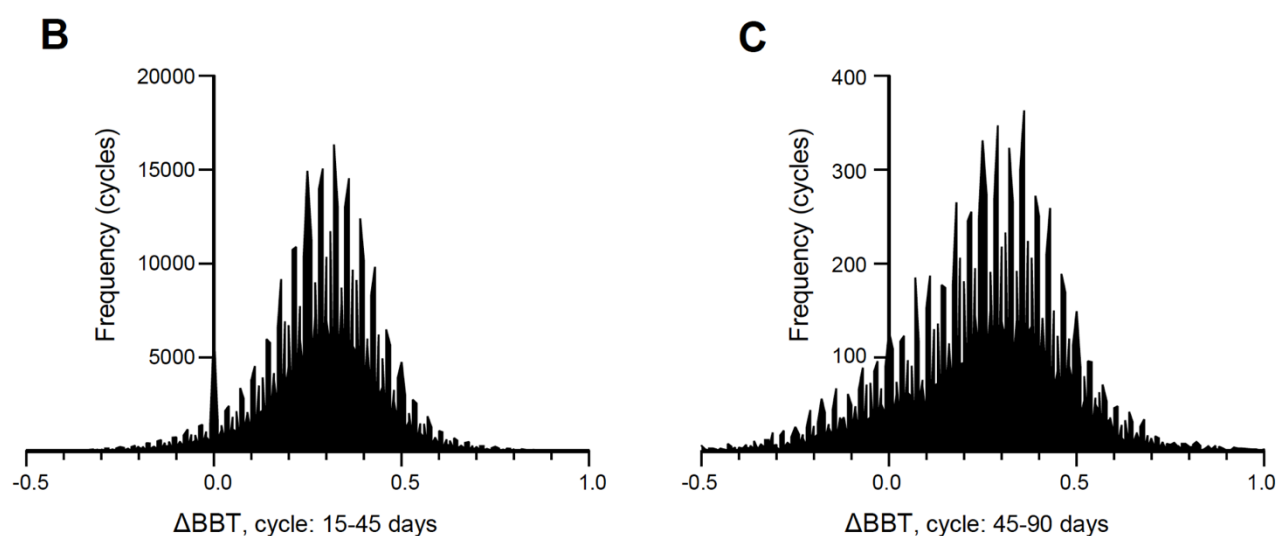
We also conducted an additional multiple regression analysis (corresponding to Table 2) with data restricted to cycles of 15–45 days (Supplemental Table 4).

Characteristic	Pearson's correlation n	<i>p</i> value*	Adjusted Std. coefficients <i>Beta</i> [†]	<i>p</i> value*	VIF
Menstrual cycle length (n = 320,067)					
Age of subjects	-.203	<.001	-.203	<.001	1.00
Average temperature	-.007	<.001	-.016	<.001	2.18
Precipitation amount	-.004	<.001	-.003	.165	1.37
Sunshine hours	.001	.418	.009	<.001	1.83
Menstrual cycle length restricted to 15-45 days (n = 307,249)					
Age of subjects	-.230	<.001	-.230	<.001	1.00
Average temperature	-.012	<.001	-.019	<.001	2.15
Precipitation amount	-.007	<.001	.000	.838	1.40
Sunshine hours	-.002	.141	.010	<.001	1.82

The total number of cycles of 15–45 days analyzed was 307,249, corresponding to about 95% of the number of cycles of 7–90 days analyzed. The results of the additional analysis were comparable to the previous analysis using the data for 7–90 days.

The above additional analysis show that the results for cycles of 15–45 days were comparable to those for cycles of 7–90 days.

Shorter or longer menstrual cycles may be caused by medical conditions such as PCOS, hypothalamic amenorrhea, and hyperprolactinemia. PCOS is the most frequent cause of rare menstruation and is known to cause anovulation/oligo-ovulation (irregular but not completely absent ovulation); however, the ratio of anovulation/oligo-ovulation is unclear (Goldrat, 2018). We next examined changes in BBT in cycles of 45–90 days, and determined if the frequency distribution differed from that for cycles of 15–45 days. If most cycles of 45–90 days were accounted for by anovulation due to PCOS, the frequency of the Δ BBT would increase around 0°C since the progesterone does not act in case of anovulation. The frequency distributions (Supplemental Figure 5B, C) are shown below.



The left figure shows the frequency of cycles of 15–45 days and the right figure shows the frequency of cycles of 45–90 days. The horizontal axis indicates Δ BBT ($^{\circ}\text{C}$) and the vertical axis indicates cycle frequency. The frequency distributions for both cycles were similar, with the peak near 0.4°C . This indicated that most women with cycles of 45–90 days probably experienced delayed ovulation (oligo-ovulation), but not anovulation. In this study, follicular body temperature was defined as the average BBT for 10 days from the start date of menstruation, and luteal phase body temperature as the average BBT for 10 days going back from the start date of the next menstruation. Recorded data for <5 days (in the 10-day window) were excluded from the dataset. We believe that the BBT data were highly credible. The variance in menstrual cycle distribution for 45–90 days was much wider than that for 15–45 days, as pointed out by reviewer, and cycles with anovulation could have been included in our dataset. However, the results suggested that more women with cycles of 45–90 days underwent ovulation, including oligo-menstruation, than generally considered by gynecologists. According to our sub-analysis, most women, including those with cycles of 45–90 days, ovulated and released progesterone. Thus, although we appreciate the reviewer's recommendation, we believe that it is still reasonable to include cycles of 45–90 days in the overall analysis.

We have added information on the possible implications for the analysis of including women with anovulation caused by PCOS, hypothalamic amenorrhea, or hyperprolactinemia. We have revised the Methods, Results and limitation sections as follows and added Supplemental Tables 3 and 4, and Supplemental Figure 5A-C.

Page 7, line 279: “Finally, we repeated all analyses on menstrual cycle length restricting the data to those on cycles with 15–45 days, since the menstrual cycle length is generally considered to be about 15–45 days.”

Page 9, line 474: “*Validation of menstrual cycle length*

Sub-analysis focusing on cycles with 15–45 days showed results similar to those from all data with cycles with 7–90 days. Age-dependent changes of menstrual cycle length were comparable with those calculated from all data (Supplemental Fig. 5A). Results from the GEE analysis (corresponding to Table 1: Supplemental Table 3) and multiple regression analysis (corresponding to Table 2: Supplemental Table 4), were also similar. Interestingly histograms on Δ BBT showed similar distributions with a peak around 0.4 °C (Supplemental Fig 5B, 5C) suggesting that most women with cycle length of 45–90 days are probably delayed ovulation (oligo-ovulation), but not anovulation.”

Page 12, line 719: “Third, we did not have data on ovulation thus our sample may have included cycles with anovulation as seen in women with PCOS, hypothalamic amenorrhea or hyperprolactinemia. However, our sub-analyses using cycle data restricted to 15–45 days also showed age-dependent change of mean cycle length and the association between external temperature and BBT, thus it is unlikely our principal findings were driven by such outliers.”

Page 16: “**Supplementary Fig. 5**

Age-dependent changes in menstrual cycle length (days) restricted to cycles of 15–45 days (A). Comparison of frequency distributions among Δ BBT and cycles of 15–45 days (B), and 45–90 days (C). Five percent trimmed means (lines) and standard deviations (shaded area) are shown.”

Comment 2: *Regarding their discussion of BBT and follicular and luteal body temperature, it is likely that the key reason that these women are recording their temperature is as a measure of ovulation, either for pregnancy promotion or prevention. Thus, as the authors write, "the biphasic nature of the menstrual cycle is a useful indicator for women who want to become pregnant." By focusing on mean follicular and luteal temperatures, the author miss the opportunity to present data on the change in temperature from the follicular to luteal phase—the extent to which this is detected among the women who recorded their temperatures, the amount of temperature change associated with bleeding x days later, variation with age and environment, etc.*

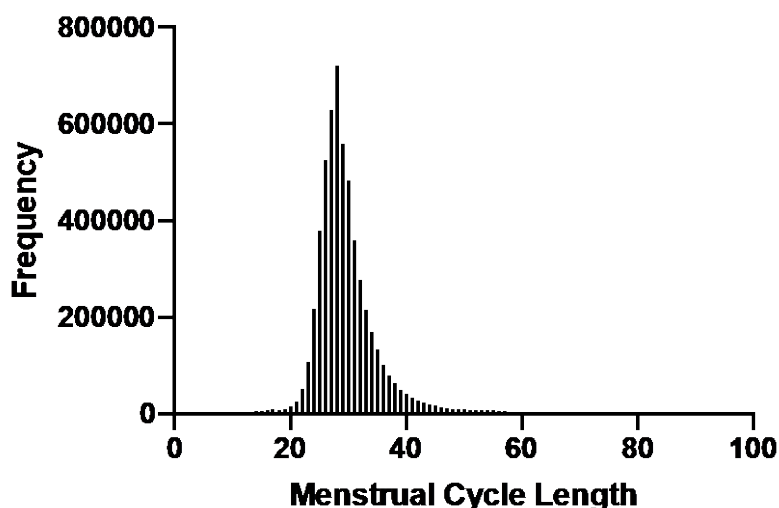
Response: In this study, we did not collect “day-by-day” body temperature data, and “day-by-day” data were aggregated by calculating the mean values. This was because “day-by-day” temperature data are more likely to include measurement errors, making rigorous assessment of ΔBBT difficult. Regarding the extent to which biphasic temperature changes were detected among the women who recorded their temperatures, we investigated the ratios of biphasic and monophasic stratified by age, defining biphasic for ΔBBT as ≥ 0.2 and monophasic for ΔBBT as ≤ 0.1 . When we aggregated data based on the eight age groups, we confirmed that most women had biphasic temperature changes, depending on their age: 15–19 years, 67%; 20–24 years, 78%; 25–29 years, 88%; 30–34 years, 91%; 35–39 years, 91%; 40–44 years, 89%; 45–50 years, 81%; and 50–54 years, 69%. We have addressed the reviewers’ concerns in the Methods and Results sections as follows.

Page 6, line 234: “Cycles with $\Delta\text{BBT} \geq 0.2$ were defined as biphasic body temperature, and those with $\Delta\text{BBT} \leq 0.1$ were defined as monophasic body temperature.”

Page 8, line 363: “The proportion of cycles with biphasic body temperature varied depending on the age group: 15–19 years, 67%; 20–24 years, 78%; 25–29 years, 88%; 30–34 years, 91%; 35–39 years, 91%; 40–44 years, 89%; 45–50 years, 81%; and 50–54 years, 69%.”

Comment 3: *Finally, regarding the statistical analysis, I have two comments. First, the authors report that menstrual cycle length did not follow a normal distribution. What was the distribution - what it skewed in one direction or the other? Does it more resemble a normal curve after restricting cycle length to a narrower window like 15 to 45 days? What is the reference for "Box-Cox" transformation and why was this particular transformation used? Second, the authors cite their own previous papers in the methodology section when commenting that generalized estimation equations were used to adjust for confounding factors and for within-person correlations of multiple records. When referring to the references given, it is stated that "we used GEE adjusting for correlations within the same patients, for a binomial family using the logit-link function," but no reference is given for the logit-link function or how it corrects for correlations within patients for a binomial family. The authors should reference the statistical paper that is the basis for this approach to analysis, and provide one or two sentences explaining the method intuitively.*

Response: Before conducting the main analysis, we carried out Kolmogorov-Smirnov tests and examined the frequency distribution to check if menstrual cycle length followed a normal distribution. The Kolmogorov-Smirnov test result ($p < .001$) indicated that menstrual cycle length was not distributed normally. The frequency distribution is shown below.



In the upper diagram, the horizontal axis indicates menstrual cycle length (days), and the vertical axis indicates the frequency of cycles. As shown in the figure the distribution has only one peak but is skewed to the right. Thus, we conducted Box-Cox transformation to alter the distribution closer to normal. Box-Cox transformation is a commonly used technique which chooses and fits a power transformation to change the distribution of a (non-normal) variable closest to normal (Box, 1964). This transformation is important so that the data does not violate the normality assumption required to fit a regression model. (Mercedes, 2007; Butler, 2015; Susana, 2018)

Next, regarding as GEE, we apologize for the lack of explanation for methodology. We used GEE based on the following references (James, 2002; James, 2003; Alan, 2010), which have been included in the revision. We used GEE using the identity-link function to take into account correlations between measurements from the same women, assuming the outcomes (transformed menstrual length and temperatures) follow a normal distribution. The reason for using GEE is to treat the same women's cycle as a hierarchical cluster. We cited two previous studies where similar hierarchical clustering was performed: one which used GEE to calculate relative ratio clustering fertility facilities (Tatsumi, 2017), and another to calculate odds ratio clustering same women who did intra-uterine insemination multiple times (Tatsumi, 2018). We have addressed the reviewers' concerns in the methods section as follows.

Page 6, line 170: “As menstrual cycle length days did not follow a normal distribution, and the mean and standard deviation (SD) were therefore calculated after Box-Cox transformation, a commonly used technique which chooses and fits a power transformation to change the distribution of a (non-normal) variable closest to normal (Box, 1964). To confirm our results, we also conducted sub-analysis where we restricted cycles to one cycle per woman to eliminate the bias related to repeated sampling. Next, generalized estimation equations (GEE) using the identity-link function to take into account within-person correlations of multiple records (James, 2003; Alan, 2010), assuming normal distribution of the outcome, and adjusting for confounding factors were conducted to

estimate the effect of age, season and year registered on mean cycle length and BBT according to our previous reports (Tatsumi, 2017; Tatsumi, 2018). To minimize the bias related to the residence such as external temperature, precipitation amount, and sunshine hours, we restricted data to 798,589 cycle data obtained in Tokyo for this analysis.”

We greatly appreciate your helpful comments.

We apologize that we cannot include all the expressions pointed out by the reviewer in the paper due to the word count limit.

References:

- O, Goldrat; A, Delbaere. PCOS: update and diagnostic approach. *Clinical Biochemistry* (2018) 62: 24–31
- Box, George EP; Cox, DR. An analysis of transformations. *Journal of the Royal Statistical Society, Series B.* (1964) 26: 2: 211–252.
- Mercedes, O; Adelheid, WO; Elaine, B; Amani, S; Chizuru, N; Jonathan, S. Development of a WHO Growth Reference for School-Aged Children and Adolescents. *Bull World Health Organ* (2007) 85;9, 660-7
- Butler et al. Growth Charts for Non-growth Hormone Treated Prader-Willi Syndrome. *Pediatrics.* (2015) 135:1, e126-135.
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- Tatsumi T, Jwa SC, Kuwahara A, Irahara M, Kubota T, Saito H. Pregnancy and neonatal outcomes following letrozole use in frozen-thawed single embryo transfer cycles. *Hum Reprod* (2017) 1;32 6:1244-8.
- Tatsumi T, Ishida E, Tatsumi K, Okada Y, Saito T, Kubota T, et al. Advanced paternal age alone does not adversely affect pregnancy or live-birth rates or sperm parameters following intrauterine insemination. *Reprod Med Biol* (2018) 17;4: 459-65.
- James, WH; Joseph MH. Generalized Estimating Equations. (2002) A CRC Press Company, Boca Raton London NewYork Washington, D.C .
- James, AH; Abdissa, N; Michael, DE; Janet EF. Statistical Analysis of Correlated Data Using Generalized Estimating Equations. *Am J Epidemiol* (2003) 157:364–375
- Alan, EH; Jennifer, A; Nancy, L; Mark, L; Sheri, AL; Nicholas, J; Tim B; William, AS S. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. *Epidemiology.* (2010) 21:4:467-74.

Reviewer #2's comment

The authors present an interesting work on menstrual cycle length using unique technologies such as an app. This is an interesting topic that has not been apparently reproduced since the late 1950's and 1960's. Overall I found this work to be reasonably well written with a clear and cogent hypothesis. While I normally do not believe that clinical questions that have already been answered should be replicated, in this case due to changes in environmental factors I think it is reasonable and the approach appears sound.

Response: We greatly appreciate the reviewer's interest in our study.

Comment 1: Lines 84-87: Because your population is so homogeneous what is the generalized applicability of your data worldwide? This is a both a strength and weakness of your work.

Response: Menstrual cycle length is known to vary slightly by approximately 0.5 days between ethnic groups (Harlow, 1997). Similarly, BBT has also demonstrated some ethnic differences (Adzika, 2016; Rising, 1995; Hori, 1977). These studies suggested that comparing values among different ethnic groups is not meaningful. As the reviewer pointed out, our sample was relatively homogenous despite differences in living environments, and it would be difficult to collect similar samples from other countries.

The major central nervous control of mammalian thermoregulation is carried out in the preoptic area of the anterior hypothalamus. Estradiol promotes vasodilation, heat dissipation, and decreased body temperature, whereas progesterone promotes reduced vasodilation, keeping warm, and increased body temperature (Nisha, 2017). These mechanisms indicate that changes in BBT may reflect hormonal variation among women. In addition, it has been suggested that changes in BBT do not depend on ethnic variation (Eleanor, 2016). Furthermore, studies in the UK, USA, and Sweden found that mean menstrual cycle length was reduced by 3 days in women from their late twenties to early forties (Bull, 2019), reinforcing the current findings that age-dependent changes in menstrual cycle length were independent of ethnic background. These results indicating that that menstrual cycle length changes according to age, and that BBT is affected by season and external temperature, could thus be applicable worldwide. We have addressed the reviewer's suggestion in the Discussion and limitation sections as follows.

Page 11, line 641: “Confirmation of our findings are anticipated in other populations, it may be difficult to find subjects living in a large variety of climates maintaining similar living habits.”

Page 12, line 726: “Fourth, this study was conducted in a single country (Japan) with relatively uniform genetic background. While it is suggested that age-dependent changing on BBT do not

depend on ethnic variations (Simonsick, 2016), and age-dependent change of mean cycle length similar to our study has been reported in a recent study that enrolled Caucasians (Bull, 2019), the menstrual cycle length and BBT are known to vary between ethnic variations (Harlow, 1997; Hori, 1977). Thus, our findings on BBT should be tested in other areas and in other ethnicities to draw reliable conclusions.”

Comment 2: *Line 91- what is the reproducibility of the data from this app? Has it been validated?*

Response: This study assumed that the user was proficient in the app and keen to enter data. The data used in the study was based on the inclusion criterion of “users who have entered more than 10 cycles in a 2-year period”, but an average of 19 menstruations was actually recorded over 24 months. The current study was based on data from users who spontaneously filled in information for their own health, which is likely to be superior to data derived from questionnaire-based surveys, or previous smartphone app-based research with less information (Bull, 2019).

For biological reasons, full reproducibility of the collected data is not possible. For example, someone may have entered data dishonestly. However, users of this app recorded their menstruation and BBT for their own purposes, such as contraception, pregnancy, or physical condition management, and there was therefore an incentive to enter the data correctly. Furthermore, there was no social desirability bias because the data were not recorded for the purposes of research.

Comment 3: *Line 158: This is awkwardly written, please address*

Response: We apologize for these confusing sentences. We have rewritten this as follows.

Page 7, line 290: “The big data was analyzed among the users ranged from 15.0 to 54.9 years, with a peak at the mid-30-year olds (Supplemental Fig. 1A).”

Comment 4: *Line 174- what is the biological explanation of the longest cycle length being at age 23*

Response: We consider the age of 23 years, at which the menstrual cycle length changes from increasing to decreasing, to be a very important age for the reproductive reasons described below. As we described in the paper, pulsatile GnRH secretion matures and sex steroid secretion increases during adolescence. The menstrual cycle length then stabilizes, and the increase in menstrual cycle length likely reflects the maturation of the HPG axis.

In 1998, O'Connor et al. reported that fecundity peaked at the age of 23 and subsequently declined (O'Connor, 1998), while Andersen et al. reported that the rate of miscarriage was lowest at the age of 23 years (Andersen, 2000). We include the relevant figures below, because their curves are very convincing.

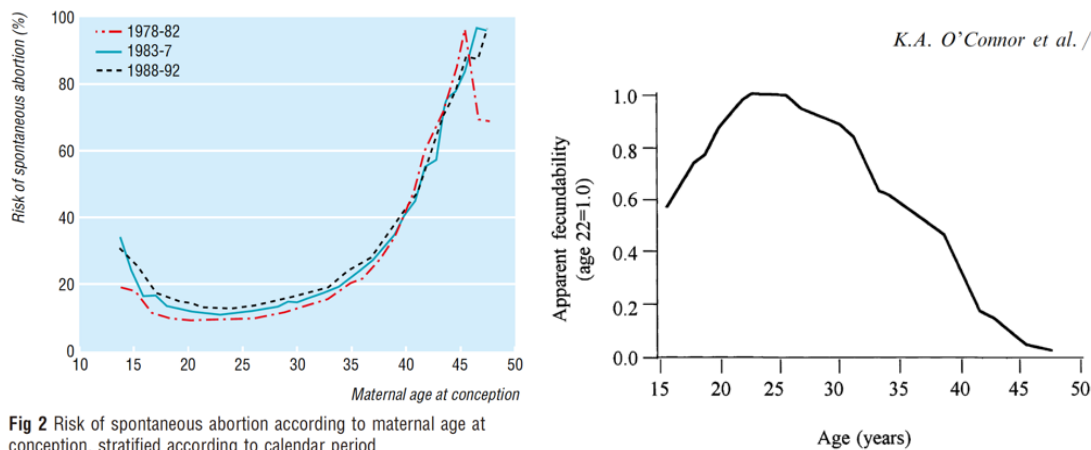


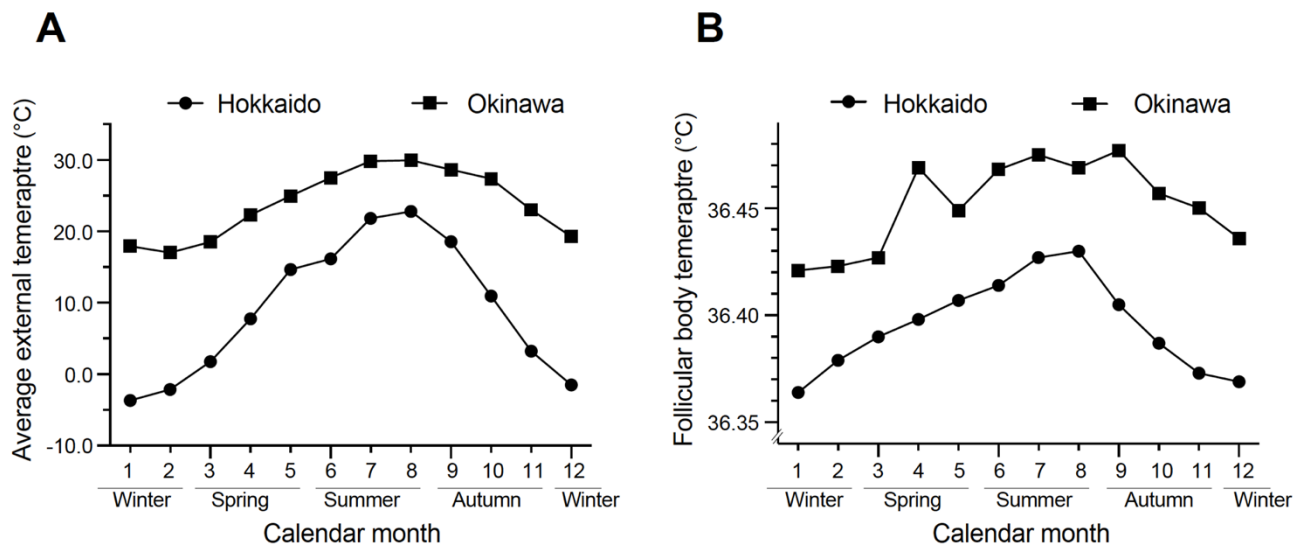
Fig 2 Risk of spontaneous abortion according to maternal age at conception, stratified according to calendar period

Based on the above data, a change in the menstrual cycle at the age of 23 reflects the maturation of hormone secretion, and indicates biological changes making the menstrual cycle more stable and increasing the chance of pregnancy. We believe that 23 years may thus be the most biologically appropriate age for human pregnancy.

Page 10, line 559: “Interestingly, the average menstrual cycle length peaked at 23 years which was consistent with the peak age of fecundability (22–23 years) (O'Connor, 1998) and the dip age for risk of miscarriage (23 years) (Andersen, 2000). This similarity implies the presence of common biological factors affecting menstrual cycle, fecundability and rate of miscarriage.”

Comment 5: Line 200-203 is the most interesting data in your set in an era when climate change is so discussed- please expand on this in your discussion

Response: We appreciate the reviewer's interest in the relationship between climate and BBT. Based on our results, we compared the external average temperatures in Hokkaido and Okinawa with the average follicular phase body temperatures of women living in these prefectures (Supplemental Figure 4).



The horizontal axis indicates calendar month, and the vertical axis indicates the external average temperature (°C), and the follicular body temperature (°C). Our results successfully reproduced the correlation between external average temperature and follicular body temperature shown in Table 2. The current study showed that, within a homogeneous population, women living in different climates had different BBTs.

BBT is associated with various factors including climate and ethnicity. Although BBT has been reported to differ between ethnic groups, these differences may be related to environmental, as well as racial differences. A lower basal body temperature was recently reported to support a slower rate of aging (Simonsick, 2016). These observations suggest that recent global warming and environmental changes throughout the world may have implications for human health and longevity.

Page 9, line 464: “Visualization of the external average temperature of Hokkaido, Okinawa and the average follicle phase body temperature of women lived in these prefectures both showed a similar seasonality. (Supplemental Fig. 4A, 4B).”

Page 11, line 641: “Confirmation of our findings are anticipated in other populations, it may be difficult to find subjects living in a large variety of climates maintaining similar living habits. While our study only suggests an association between climate and women’s health, a recent study reported that a lower basal body temperature can support a slower rate of aging (Simonsick, 2016). Such findings raise an alarm that recent global warming and environmental changes throughout the world may have impacts on human health and longevity.”

Page 16: “Supplementary Fig. 4

External average temperatures in Hokkaido and Okinawa (A) and average follicular phase body temperatures of women in those prefectures (B).”

Comment 6: *The figures are well done and easy to understand*

Response: Thank you very much for your positive comment. In making this figure, we made many different types of figures and discussed which ones were more applicable to understand what we mentioned.

We greatly appreciate your helpful comments.

We apologize that we cannot include all the expressions pointed out by the reviewer in the paper due to the word count limit.

References:

Harlow, SD; Campbell, B; Lin, X; Raz, J. Ethnic differences in the length of the menstrual cycle during the postmenarcheal period. *Am J Epidemiol.* (1997) 1;146:7:572-80.

PA Adzika Nsatimba, K Pathak, MJ Soares. Ethnic differences in resting metabolic rate, respiratory quotient and body temperature: a comparison of Africans and European Australians *Eur J Nutr* (2016) 55:1831–1838

Rising R , Fontvieille AM, Larson DE, Spraul M, Bogardus C, Ravussin E. Racial difference in body core temperature between Pima Indian and Caucasian men. *Int J Obes Relat Metab Disord.* (1995) 19:1, 1-5.

Hori S, Ohnaka M, Shiraki K, Tsujita J, Yoshimura H, Saito N, Panata M. Comparison of physical characteristics, body temperature and basal metabolism between Thai and Japanese in a neutral temperature zone. *Jpn J Physiol.* (1977); 27,5: 525-38.

Nisha Charkoudian; Emma CJ Hart; Jill N Barnes; Michael J Joyner. Autonomic control of body temperature and blood pressure: influences of female sex hormones. *Clin Auton Res* (2017) 27:149–155

Eleanor M Simonsick, Helen CS Meier, Nancy Chiles Shaffer, Stephanie A Studenski, Luigi Ferrucci. Basal body temperature as a biomarker of healthy aging. *AGE* (2016) 38:445–454

Bull JR, Rowland SP, Scherwitzl EB, Scherwitzl R, Danielsson KG, Harper J. Real-world menstrual cycle characteristics of more than 600,000 menstrual cycles. *NPJ digital medicine* (2019) 2:83.

Kathleen A. O'Connor, Darryl J. Holman, James W. Wood. Declining fecundity and ovarian ageing in natural fertility populations. *Maturitas* (1998) 30: 127–136

Anne-Marie N Andersen, J Wohlfahrt, P Christens, J Olsen, M Melbye. Maternal age and fetal loss: population based register linkage study. *BMJ* (2000) 320:24.

Simonsick EM, Meier HCS, Shaffer NC, Studenski SA, Ferrucci L. Basal body temperature as a biomarker of healthy aging. *Age*. (2016) 38:5-6:445-54.

Reviewer #3's comment

This study assesses basal body temperature and cycle length in a large number of Japanese women who entered data on a smart phone app. Reassessment of the characterization of the menstrual cycle compared to data obtain more than 50 - 80 year ago has value. This study does add information about gaps in our knowledge on the subject regarding effect of temperature and season, but generally does not add novel or new information.

Response: We greatly appreciate your helpful comments.

Comment 1: *Limitations include lack of rationale of the importance or biological significance of basal body temperature in the follicular and luteal phase.*

Response: In line with the reviewer's comment, the American Society for Reproductive Medicine (committee opinion, 2012) stated that "because of the inconvenience to patients, the measurement of BBT is of historical significance only and should be discouraged." However, BBT may provide information on progesterone secretion, and may be useful for women who can rarely visit an infertility clinic. Compared with previous studies based on the committee opinion, our dataset included much larger sample sizes of women and cycles, and this big-data analysis may thus be able to reveal novel relationships.

We investigated the ratio of biphasic and monophasic BBTs stratified by age, defining cycles with $\Delta\text{BBT} \geq 0.2$ as biphasic and those with $\Delta\text{BBT} \leq 0.1$ as monophasic. When we aggregated data based on the eight age groups, we confirmed that most women had biphasic temperature changes, depending on their age: 15–19 years, 67%; 20–24 years, 78%; 25–29 years, 88%; 30–34 years, 91%; 35–39 years, 91%; 40–44 years, 89%; 45–50 years, 81%; and 50–54 years, 69%. We have addressed the reviewer's concerns in the Methods and Discussion sections as follows.

Page 6, line 234: "Cycles with $\Delta\text{BBT} \geq 0.2$ were defined as biphasic body temperature, and those with $\Delta\text{BBT} \leq 0.1$ were defined as monophasic body temperature."

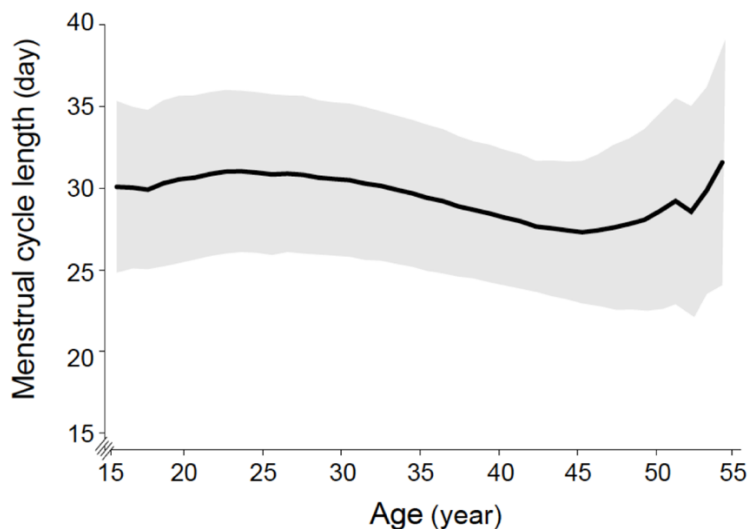
Page 8, line 363: "The proportion of cycles with biphasic body temperature varied depending on the age group: 15–19 years, 67%; 20–24 years, 78%; 25–29 years, 88%; 30–34 years, 91%; 35–39 years, 91%; 40–44 years, 89%; 45–50 years, 81%; and 50–54 years, 69%."

Page 10, line 329: "Although the American Society for Reproductive Medicine reported that the use of BBT should be discouraged because of its inconvenience and because it was not useful for determining luteal phase deficiency (committee opinion, 2012), the biphasic nature of the menstrual cycle is a useful indicator for women who want to become pregnant."

Comment 2: *The study does not before any sensitivity analysis such as restriction to only one cycle per person, or assessment of cycle in the same women.*

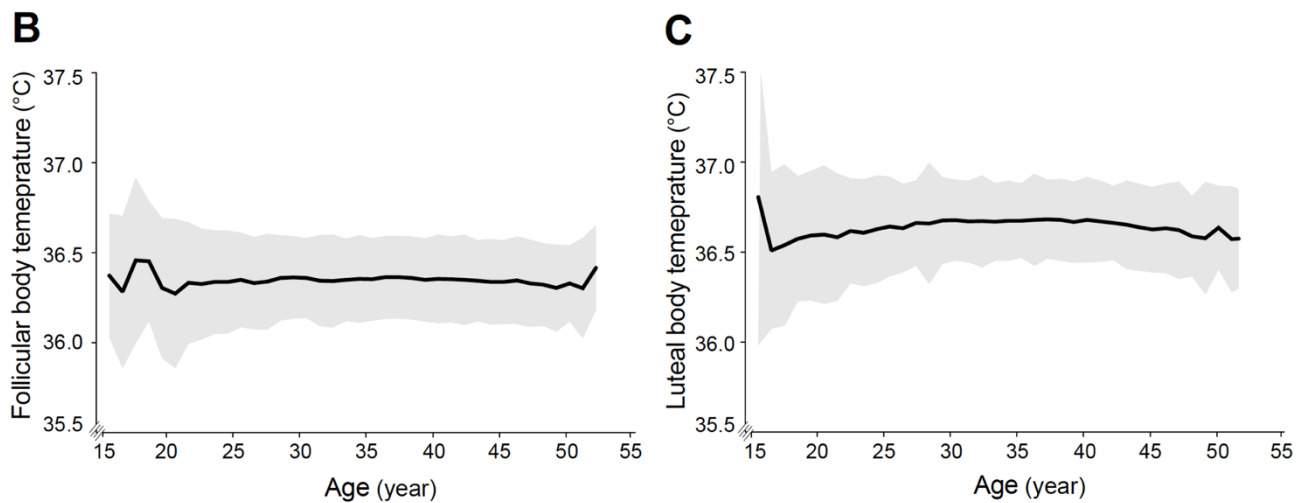
Response: As the reviewer points out, the study did not restrict the analysis to one cycle per woman, and the same women could thus be included for up to 24 cycles (2 years), which may affect the analyses of menstrual cycle length and BBT. We therefore carried out additional analyses restricted to one cycle per woman to eliminate the effects of multiple entries of cycles from the same woman. The total number of cycles analyzed was 310,668, which represented 1/19 of the total number of recorded cycles. Supplemental Figure 3A is shown below.

A



In the upper diagram, the horizontal axis indicates age (years) and the vertical axis indicates the menstrual cycle length. The curve in revised Figure 1 was slightly distorted, but no significant change was observed. As in the original figure, the longest mean menstrual cycle (31.05 days) was observed in women aged 23 years.

We also examined changes in BBT as shown below.



In the upper diagram, the left figure (Supplemental Figure 3B) shows follicular body temperature and the right figure (Supplemental Figure 3C) shows luteal body temperature. The horizontal axis indicates age (years) and the vertical axis indicates follicular and luteal body temperatures, respectively ($^{\circ}\text{C}$). Regarding BBT, the average follicular body temperature showed no significant age-dependent changes, while luteal body temperature showed an age-dependent change, as shown in the previous figures.

The above results restricted to one cycle per women showed no significant difference compared with the analysis including all cycles. We have mentioned this sub-analysis in the Results section.

Next, we used generalized estimation equations (GEE) to assess the same women's cycles. GEE was identified by Harrison and Hulin in 1989 as an analytical tool for organizational research, and was subsequently developed by Zeger and Liang for regression analysis of longitudinal or repeated measures research. We used GEE adjusting for correlations within the same women, for normal distribution, and using the identity-link function. GEE was used to treat the same women's cycles as a hierarchical cluster, citing two previous reports using similar hierarchical clustering: to calculate relative ratio clustering fertility facilities (Tatsumi, 2017), and to calculate odds ratio clustering among women who performed IUI multiple times (Tatsumi, 2018). In the current study, we confirmed significant effects of age on cycle length and luteal body temperature using GEE-based analysis adjusting for cycles within the same women. We have addressed the reviewer's concerns in the Results sections as follows.

Page 8, line 361: “Sub-analysis that restricted cycles with one cycle per woman to eliminate the bias related to repeated sampling showed results similar to those obtained from all cycle data (Supplemental Fig. 3A-C).”

Page 16: “Supplementary Fig. 3

Age-dependent changes in menstrual cycle length (A), follicular phase temperature (B), and luteal phase temperature (C) restricted to one cycle per woman. Five percent trimmed means (lines) and standard deviations (shaded area) are shown.”

Comment 3: *The study is essentially cross sectional so care much be taken regarding verbs like continuous changes over time or age.*

Response: We agree with the reviewer’s suggestion. The current study was a cross-sectional study and suggestions of continuous changes over time or age are therefore inappropriate. We have revised the Abstracts, Results, and Discussion sections as follows.

Page 3, line 71: “The mean menstrual cycle length increased from age 15 to 23 years, subsequently decreased up to age 45 years, and then increased again.”

Page 3, line 74: “A significant association between external temperature and body temperature (follicular and luteal) was observed, though menstrual cycle length did not show such an association.”

Page 8, line 350: “An increase in menstrual cycle length was observed from age 15 to the early 20s. The longest mean menstrual cycle length of 30.7 days was observed at age 23 years, this then decreased to 27.3 days at 45 years, and then increased.”

Page 9, line 458: “...indicating that BBT was associated with environmental factors.”

Page 9, line 484: “We observed in our present study that menstrual cycle length changed with age, while it was not associated with season or other climatic factors. Luteal, but not follicular, body temperature changed with age, and both follicular and luteal phase BBTs were associated with environmental temperature.”

Page 12, line 712: “First, there could be selection bias associated with being an active app user.”

Page 12, line 732: “Our study found that menstrual cycle length and BBT, both of which were previously considered to be stable, are associated with age and external environment.”

Comment 4: *The generalizability of the study is low give the homogeneity of the population.*

Response: Menstrual cycle length is known to vary slightly by approximately 0.5 days between ethnic groups (Harlow, 1997). Similarly, BBT has also demonstrated some ethnic differences (Adzika, 2016; Rising, 1995; Hori, 1977). These studies suggested that comparing values among different ethnic groups is not meaningful. As the reviewer pointed out, our sample was relatively homogenous despite differences in living environments, and it would be difficult to collect similar samples from other countries.

The major central nervous control of mammalian thermoregulation is carried out in the preoptic area of the anterior hypothalamus. Estradiol promotes vasodilation, heat dissipation, and decreased body temperature, whereas progesterone promotes reduced vasodilation, keeping warm, and increased body temperature (Nisha, 2017). These mechanisms indicate that changes in BBT may reflect hormonal variation among women. In addition, it has been suggested that changes in BBT do not depend on ethnic variation (Eleanor, 2016). Furthermore, studies in the UK, USA, and Sweden found that mean menstrual cycle length was reduced by 3 days in women from their late twenties to early forties (Bull, 2019), reinforcing the current findings that age-dependent changes in menstrual cycle length were independent of ethnic background. These results indicating that that menstrual cycle length changes according to age, and that BBT is affected by season and external temperature, could thus be applicable worldwide.

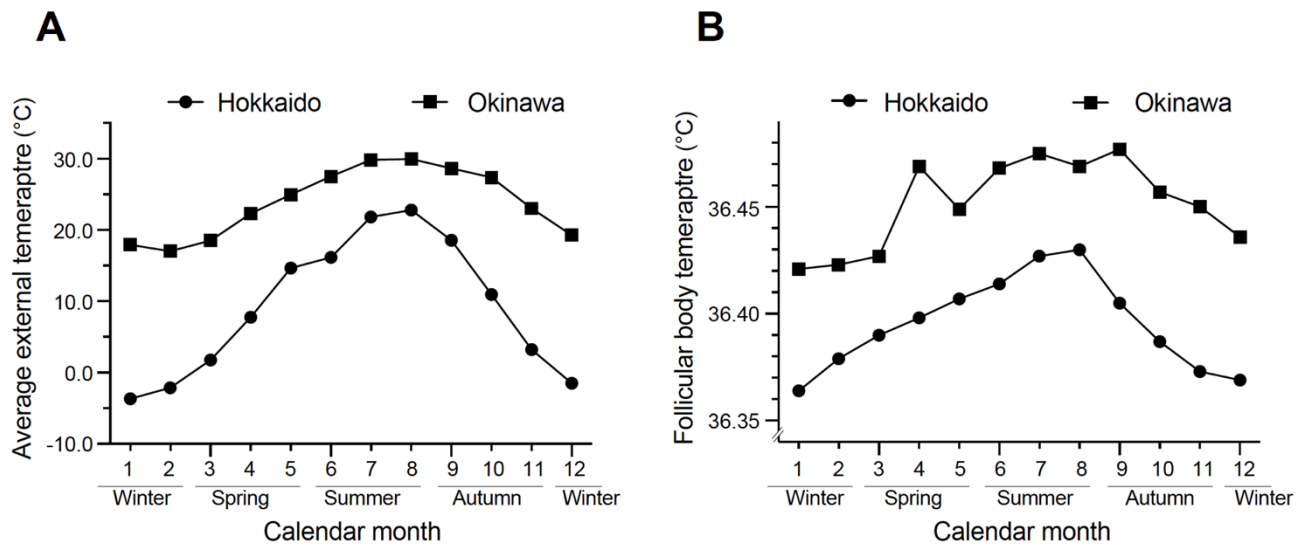
We have addressed the reviewer's concerns in the limitations section as follows.

Page 12, line 726: “Fourth, this study was conducted in a single country (Japan) with relatively uniform genetic background. While it is suggested that age-dependent changing on BBT do not depend on ethnic variations (Simonsick, 2016), and age-dependent change of mean cycle length similar to our study has been reported in a recent study that enrolled Caucasians (Bull, 2019), the menstrual cycle length and BBT are known to vary between ethnic variations (Harlow, 1997; Hori, 1977). Thus, our findings on BBT should be tested in other areas and in other ethnicities to draw reliable conclusions.”

Comment 5: *Table 1 and 2 are statistically correct, but lack clinical interpretability While this is an interesting use of big data, it unfortunately does not add substantially to current understanding of the menstrual cycle.*

Response: We apologize that the results shown in Table 1 are difficult to interpret. The reason we place Table 1 is to examine the validity of Figure 1. We used data from one city, Tokyo, to minimize the effects of bias related to the environment on menstrual cycle length and BBT. In addition, as in our response to Comment 2, we conducted GEE to determine if menstrual cycle length and BBT changed with age and season, accounting for multiple inclusions of the same women. As shown in Table 1, we confirmed that the original figure was valid.

Next, we investigated the clinical interpretability of Table 2. Based on the results showing that luteal, but not follicular phase temperature was associated with age, we compared the external average temperatures in Hokkaido and Okinawa with the average follicular phase body temperatures of women in those prefectures.



The horizontal axis indicates calendar month, and the vertical axis indicates the external average temperature (°C), and the follicular body temperature (°C). Our results successfully reproduced the correlation between external average temperature and follicular body temperature shown in Table 2. The current study showed that, within a homogeneous population, women living in different climates had different BBTs.

Page 9, line 272: “Visualization of the external average temperatures in Hokkaido and Okinawa and the average follicular phase body temperatures of women living in these prefectures showed similar seasonalities (Supplemental Fig. 4A, B).”

Page 17: “Supplementary Fig. 4

External average temperatures in Hokkaido and Okinawa (A) and average follicular phase body temperatures of women in those prefectures (B).”

We greatly appreciate your helpful comments.

We apologize that we cannot include all the expressions pointed out by the reviewer in the paper due to the word count limit.

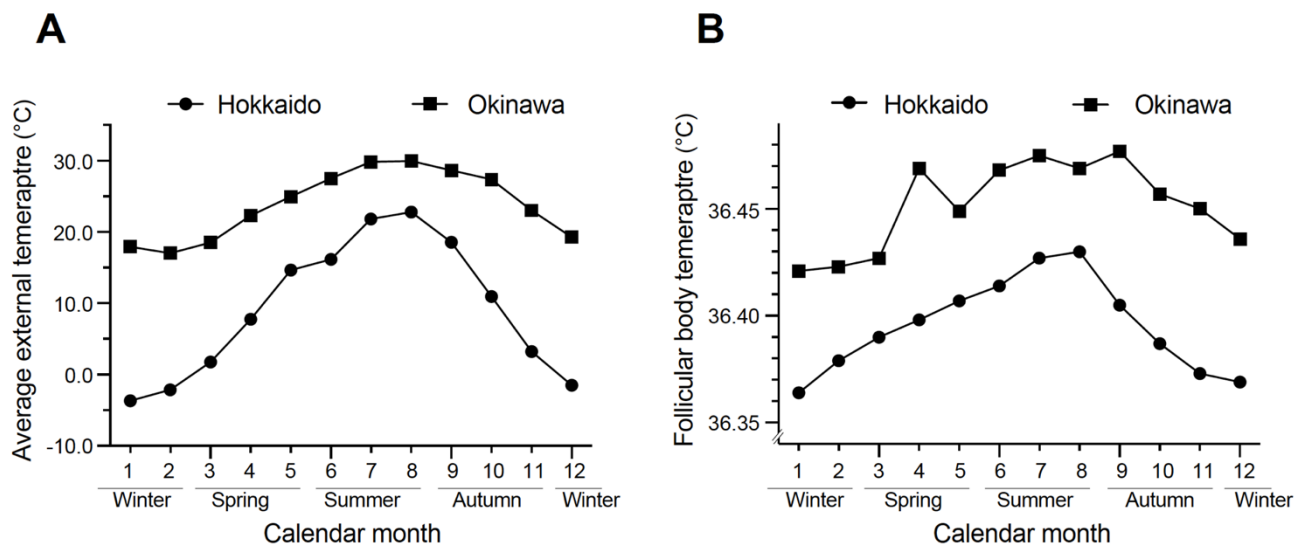
References:

- Practice Committee of the American Society for Reproductive Medicine, Current clinical irrelevance of luteal phase deficiency: a committee opinion. *Fertil Steril* (2015)103, e27-32.
- Tatsumi T, Jwa SC, Kuwahara A, Irahara M, Kubota T, Saito H. Pregnancy and neonatal outcomes following letrozole use in frozen-thawed single embryo transfer cycles. *Hum Reprod* (2017) 1;32 6:1244-8.
- Tatsumi T, Ishida E, Tatsumi K, Okada Y, Saito T, Kubota T, et al. Advanced paternal age alone does not adversely affect pregnancy or live-birth rates or sperm parameters following intrauterine insemination. *Reprod Med Biol* (2018) 17;4: 459-65.
- Harlow, SD; Campbell, B; Lin, X; Raz, J. Ethnic differences in the length of the menstrual cycle during the postmenarcheal period. *Am J Epidemiol.* (1997) 1;146:7:572-80.
- PA Adzika Nsatimba, K Pathak, MJ Soares. Ethnic differences in resting metabolic rate, respiratory quotient and body temperature: a comparison of Africans and European Australians *Eur J Nutr* (2016) 55:1831–1838
- Rising R , Fontvieille AM, Larson DE, Spraul M, Bogardus C, Ravussin E. Racial difference in body core temperature between Pima Indian and Caucasian men. *Int J Obes Relat Metab Disord.* (1995) 19,1:1-5.
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- Nisha Charkoudian; Emma CJ Hart; Jill N Barnes; Michael J Joyner. Autonomic control of body temperature and blood pressure: influences of female sex hormones. *Clin Auton Res* (2017) 27:149–155
- Eleanor M Simonsick, Helen CS Meier, Nancy Chiles Shaffer, Stephanie A Studenski, Luigi Ferrucci. Basal body temperature as a biomarker of healthy aging. *AGE* (2016) 38:445–454
- Bull JR, Rowland SP, Scherwitzl EB, Scherwitzl R, Danielsson KG, Harper J. Real-world menstrual cycle characteristics of more than 600,000 menstrual cycles. *NPJ digital medicine* (2019) 2:83.

Statistical Editor's comments

Comment 1: While Tables 1, 2, 3 show many statistically significant associations of temp vs age, season, average temp, precipitation or sunshine, the correlations are actually quite weak. That is, they are statistically significant owing to the large sample, but would have wide variability for prediction in an individual case. Therefore, the figures, which are useful for summarizing the data, show how wide the variability is.

Response: We agree that the correlations are quite weak. We therefore investigated the clinical interpretability of Table 2. Based on the results showing that luteal, but not follicular phase, temperature was associated with age, we compared the external average temperatures in Hokkaido and Okinawa with the average follicular phase body temperatures of women in those prefectures.



The horizontal axis indicates calendar month, and the vertical axis indicates the external average temperature (°C), and the follicular body temperature (°C). Our results successfully reproduced the correlation between external average temperature and follicular body temperature shown in Table 2. The current study showed that, within a homogeneous population, women living in different climates had different BBTs.

Page 9, line 464: “Visualization of the external average temperature of Hokkaido, Okinawa and the average follicle phase body temperature of women lived in these prefectures both showed a similar seasonality. (Supplemental Fig. 4A, 4B).”

Page 16: “**Supplementary Fig. 4**

External average temperatures in Hokkaido and Okinawa (**A**) and average follicular phase body temperatures of women in those prefectures (**B**).”

Comment 2: *Also, as acknowledged by the Authors, the data missing re: wgt or BMI may have been important covariates that affect body temp.*

Response: As the editor points out, body weight and height were unfortunately not necessarily input in our app data. Given that BBT may have been affected by weight and height, we have revised the limitations section as follows.

Page 12, line 716: “Second, most cycle data in our app lacked information on body size (*i.e.*, height and weight), resulting in decreased power to detect potential effect(s) of body size on cycle length and BBT. While larger studies are warranted to confirm our result that there is no relationship between body size and cycle length, this could be true considering the fact that height/weight are not involved in irregular menstrual cycles in PCOS (Elting, 2000).”

Comment 3: *Also, these data re: months of year are applicable to the Northern Hemisphere and presumably would be reversed in the Southern hemisphere and may be influenced generally by latitude.*

Response: As the editor points out, the study was conducted in the northern hemisphere and the seasons would be reversed in the southern hemisphere, and the results could be affected by latitude. We have added an explanation of the seasons to Figure 2 and supplemental Fig 4 to clarify this point.

Comment 4: *Finally, the data show the importance of individual women recording serial data to determine their own profile of temp during menstrual cycle.*

Response: We greatly appreciate this important comment and have added an additional explanation to the Discussion accordingly.

Page 12, line 732: “Additionally, our study shows how recording of serial health data may not only help the individual but lead to better understanding of women’s reproductive health.”

We thank the statistical editor for their helpful and constructive comments, which have allowed us to improve our paper.

References:

Elting MW, Korsen TJ, Rekers-Mombarg LT, Schoemaker J. Women with polycystic ovary syndrome gain regular menstrual cycles when ageing. *Hum Reprod* (2000);15.1:24-8.

Editor's comments

Comment 1: *Line 42: The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstracts conclusion. Precis should be the "hook" for people who scan the Table of Contents to see what to read. It shouldn't not include statements like "in this study" or "we found". Just state what you found. Also, please eliminate the statement that “This is novel as it is not relevant for the précis.*

Response: Thank you for your advice. We have revised the précis accordingly.

Page 2, line 53: “Our smartphone app-based analysis of 6 million menstrual cycles among Japanese women found age-dependent and seasonal changes of cycle length and BBT.”

Comment 2: *In the manuscript, this would be considered a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the data bases you have searched (PubMed, Google Scholar, EMBASE for example) and the search terms used. IF not done, please edit it out of the paper.*

Response: We agree that these claims were inappropriate and have removed them accordingly.

Page 10, line 541: “We analyzed 6 million menstrual cycle data derived from 320,000 active app users to add to current knowledge concerning characteristics associated with cycle length and BBT.”

Page 10, line 557: “Collectively, we demonstrated age-dependent change in menstrual cycle length, from relatively short in the teens, stable in the 20s, shortened in the 30s and early 40s, and patchy in the 50s.”

Page 11, line 641: “Confirmation of our findings are anticipated in other populations, it may be difficult to find subjects living in a large variety of climates maintaining similar living habits.”

Comment 3: *Please add the unit of measure of cycle length in the abstract, and if not present there, in the manuscript and tables as well.*

Response: We apologize for this omission and have added the unit of cycle length (days) in the revised manuscript and tables accordingly.

Page 3, line 71: “The mean menstrual cycle length increased from age 15 to 23 years, subsequently decreased up to age 45 years, and then increased again. Average follicular body temperature showed no significant age-dependent changes, but luteal body temperature gradually increased up to 29 years, then stabilized, and started to decrease after age 42 years.”

Page 8, line 350: “An increase in menstrual cycle length was observed from age 15 to the early 20s. The longest mean menstrual cycle length of 30.7 days was observed at age 23 years, this then decreased to 27.3 days at 45 years, and then increased.”

Comment 4: *Line 59: Should read “temperature WHICH showed no significant change....”*

Response: According to the editor’s suggestion and to improve readability, we altered the sentence as follows.

Page 3, line 72: “Average follicular body temperature showed no significant age-dependent changes, but luteal body temperature gradually increased up to 29 years, then stabilized, and started to decrease after age 42 years.”

Comment 5: *Line 61 includes causal language (...temperature did not affect....). Here and throughout your paper, this should be replaced with associative language. As an observational trial, you can not demonstrate causation.*

Response: We agree that causal language is inappropriate and have revised the entire manuscript accordingly.

Page 3, line 71: “The mean menstrual cycle length increased from age 15 to 23 years, subsequently decreased up to age 45 years, and then increased again.”

Page 3, line 74: “A significant association between external temperature and body temperature (follicular and luteal) was observed, though menstrual cycle length did not show such an association.”

Page 8, line 350: “An increase in menstrual cycle length was observed from age 15 to the early 20s. The longest mean menstrual cycle length of 30.7 days was observed at age 23 years, this then decreased to 27.3 days at 45 years, and then increased.”

Page 9, line 458: "...indicating that BBT was associated with environmental factors."

Page 9, line 484: "We observed in our present study that menstrual cycle length changed with age, while it was not associated with season or other climatic factors. Luteal, but not follicular, body temperature changed with age, and both follicular and luteal phase BBTs were associated with environmental temperature."

Page 12, line 712: "First, there could be selection bias associated with being an active app user."

Page 12, line 732: "Our study found that menstrual cycle length and BBT, both of which were previously considered to be stable, are associated with age and external environment."

Comment 6: *Line 63: Instead of "big data" please state something like "data self-entered into a smart phone application"*

Response: According to the editor's suggestion, we have revised the manuscript as follows.

Page 3, line 67: "These results derived from data self-entered into a smart phone application revealed under-recognized age-dependent and seasonal changes in menstrual cycle length and BBT, which will contribute to a better understanding of women's reproductive health in the modern world."

Comment 7: *Line 69: Perhaps "Current understanding of menstrual cycle length and basal body temperature is based on...". Also, "knowledge" should be singular, not plural.*

Response: According to the editor's suggestion, we have revised the manuscript as follows.

Page 4, line 134: "Current understanding of menstrual cycle length and basal body temperature (BBT) is largely based on the knowledge that was drawn from small descriptive studies performed in the 1950s."

Comment 8: *Line 80 Instead of "interesting" perhaps substitute "unknown".*

Response: According to the editor's suggestion, we have revised the manuscript as follows.

Page 4, line 146: "...the effects of the regional environment and season on human health and longevity remain unknown."

Comment 9: *Line 93: Basic functions...ARE freely available...*

Response: According to the editor's suggestion, we have revised the manuscript as follows.

Page 4, line 158: "The basic functions of this app are freely available on the Android and iOS platforms, and it is currently downloaded by more than 14 million women as the most popular women's health care service in Japan."

Comment 10: *Line 118: Instead of "kids" please state "greater than 5 children"*

Response: According to the editor's suggestion, we have revised the manuscript as follows.

Page 5, line 202: "....and greater than 5 children (89 cycles),"

Comment 11: *Line 127: One of your reviewers suggests eliminating cycles that could be related to PCOS. I'm not sure how you would do this in reality so I'm not in favor of you making that change. Perhaps doing a subanalysis of cycles from 45-90 days makes some sense, however, as anovulatory bleeding from what ever cause may be more likely to fall into this time frame and should not really be considered a "menstrual cycle".*

Response: Please see our response to Reviewer 1's Comment 1 above.

Comment 12: *Did you collect contraceptive information? This should be added, if not, as many forms of contraception influence cycle length. Without this information, unfortunately, this paper may not be acceptable.*

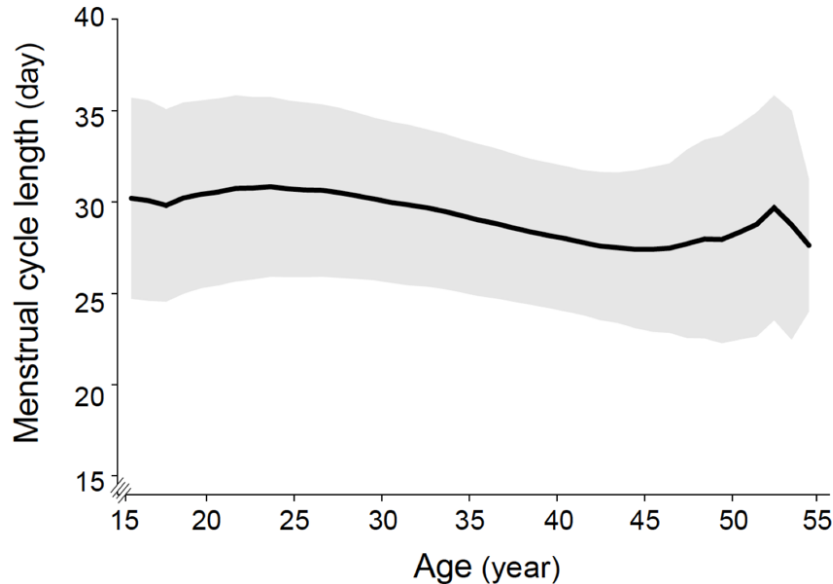
Response: Luna Luna includes information on oral contraceptive pill (OCP) use based on daily use, rather than by cycle. We therefore considered the possibility that information on pill use might be unreliable, e.g., as a result of women only checking the pill-use item for a few days in the cycle. In this study, our analysis focused on the base characteristics and values of menstrual cycle days and

basal body temperature, which were considered to be highly credible, and excluded daily data including pill use.

The main purpose of the app is to predict menstruation, and OCP users would be able to determine this based on the pill sheet, making menstruation prediction by the app almost meaningless. In an interview, Luna Luna also reported that users did not use the app when using the pill. Luna Luna has recently been updated (2019), and OCP users now only need to check whether or not the pill is being taken each cycle.

In addition, the OCP was launched as a contraceptive in Japan 1999. However, OCP use in Japan is not widespread, and only 1.0% of Japanese women use OCP as a contraceptive method (Yoshida, 2016). The most common reason for not wanting to use OCP was worries over side effects (49.8%), reflecting the Japanese characteristic of worrying about excessive side effects. These data suggest that few app users were likely to use the OCP, and this would therefore have no significant effect on the results.

The major advantage of the current study was the inclusion of data for many women who did not want to become pregnant. However, we also repeated the analysis restricted to women who wished to become pregnant as follows.



In the upper diagram, the horizontal axis indicates age (years) and the vertical axis indicates menstrual cycle length (days). When restricted to cycles of women who wanted to become pregnant, a total of 2,243,076 cycles were analyzed, compared with the total of 5,956,886 cycles. The longest mean menstrual cycle length (30.85 days) was observed at age 23 years. The curve of cycle length showed relatively less variance around the mean, as indicated by the reviewer, but no significant change compared with the overall analysis.

A version of Table 1 restricted to women who wanted to become pregnant is shown below.

Characteristic	Menstrual cycle length (n = 798,589)		Menstrual cycle length restricted to women wanting to be pregnant (n = 325,166)	
	95% CI [†]	p value*	95% CI [†]	p value*
Age (year)				
≤19	Reference		Reference	
20–24	.327 – .682	<.001	.355 – .826	.435
25–29	.272 – .621	<.001	.507 – .629	.834
30–34	-.325 – .021	.085	-1.16 – .031	.039
35–39	-1.32 – -.970	<.001	-2.15 – -1.02	<.001
40–44	-2.37 – -2.02	<.001	-3.10 – -1.97	<.001
45–49	-2.51 – -2.14	<.001	-3.33 – -2.15	<.001
≥50	-1.23 – -.604	<.001	-2.61 – -.601	.002
Season				
Spring	.008 – .054	.009	-.109 – .039	<.001
Summer	-.063 – -.016	.001	-.174 – -.101	<.001
Autumn	-.029 – .019	.698	-.121 – .046	<.001
Year				
2016	Reference		Reference	
2017	-.086 – -.039	<.001	-.106 – -.028	.001

A total of 325,166 cycles were analyzed from women who wanted to become pregnant, representing a decrease of approximately 470,000 cycles from the overall analysis. There was no significant change in the results of the sub-analysis compared with the base analysis, and the effect of age on cycle length was shown by GEE-based analysis.

A version of Table 2 restricted to women who wanted to become pregnant is shown below.

Characteristic	Pearson's correlation	p value*	Adjusted Std. coefficients <i>Beta</i> [†]	p value*	VIF
Menstrual cycle length (n = 320,067)					
Age of subjects	-.203	<.001	-.203	<.001	1.00
Average temperature	-.007	<.001	-.016	<.001	2.18
Precipitation amount	-.004	<.001	-.003	.165	1.37
Sunshine hours	.001	.418	.009	<.001	1.83

Menstrual cycle length restricted to whom want to be pregnant (n = 122,314)					
Age of subjects	-.200	<.001	-.199	<.001	1.00
Average temperature	-.023	<.001	-.024	<.001	2.06
Precipitation amount	-.017	<.001	-.004	.194	1.40
Sunshine hours	.001	.313	.013	<.001	1.71

A total of 122,314 cycles were analyzed for women who wanted to become pregnant, representing a decrease of approximately 200,000 cycles from the overall analysis. We found no correlation between climatic factors and cycle length.

In general, we considered that it was unlikely that women taking the OCP would record their BBT. In accordance with this, our sub-analysis revealed that the results remained unchanged in a sub-analysis restricted to women who wanted to become pregnant.

However, we agree that the lack of OCP information represents a significant limitation and have added these concerns to the limitations section as follows.

Page 12, line 723: “Similarly, it is possible our sample included cycle data obtained from those taking oral contraceptive pill (OCP). However, considering the very low proportion of OCP usage for contraception in Japanese women (1.0%) (Yoshida, 2016), we believe the effect of data derived from OCP user would be minimal.”

Comment 13: *Line 159 Peak in mid-30’s. Please add units for age throughout.*

Response: According to the editor’s suggestion, we have revised the manuscripts as follows.

Page 7, line 290: “The big data was analyzed among the users ranged from 15.0 to 54.9 years, with a peak at the mid-30-year olds (Supplemental Fig. 1A).”

Comment 14: *Please limit age, Cycle length, BMI to 1 decimal. Taking that data to the 100’s place does not really convey any useful clinical information.*

Response: According to the editor’s suggestion, we have revised the indicated values to a single decimal place.

Page 7, line 297: “Married subjects or subjects with partner(s) were older than unmarried subjects or subjects without partners (mean age 30.8 vs 25.5, 29.9 vs 27.7, respectively). The mean body mass

index of the subjects was $22.8 \pm 4.1 \text{ kg/m}^2$, and there was no relationship between cycle length and height (Supplemental Fig. 2A) or weight (Supplemental Fig. 2B)."

Page 8, line 351: "The longest mean menstrual cycle length of 30.7 days was observed at age 23 years, this then decreased to 27.3 days at 45 years, and then increased."

Comment 15: *Line 176: the value increased rather than "turned upward".*

Response: According to the editor's suggestion, we have revised this phrase accordingly.

Page 8, line 351: "The longest mean menstrual cycle length of 30.7 days was observed at age 23 years, this then decreased to 27.3 days at 45 years, and then increased."

Comment 16: *Line 204 as written does not make sense. Do you mean "We found no correlation between climatic factors and cycle length" or may "There was little association between climatic factors and cycle length"?*

Response: We apologize for this confusion and have revised the sentence as follows.

Page 9, line 467: "There was little association between climatic factors and cycle length."

Comment 17: *Line 224 :Instead of "alleviate" perhaps "stabilize" or "Improve"?*

Response: According to the editor's suggestion, we have revised the sentence as follows.

Page 9, line 551: "... which stabilizes in their 30s (26, 27)."

Comment 18: *Line 231: Perhaps "These findings are in agreement with..."*

Response: According to the editor's suggestion, we have revised this sentence as follows.

Page 10, line 558: "These findings are in agreement with current knowledge on physiology and pathology involving the menstrual cycle."

Comment 19: Lines 247: fewer” than what? And likewise, line 249 “more” than what?

Response: According to the editor’s suggestion, we have revised the manuscript as follows.

Page 11, line 638: “Hokkaido, the northernmost region, has a subarctic climate with large temperature differences from month to month and lower annual precipitation and ultraviolet irradiation, while Okinawa, as the southernmost region, has a subtropical, always warm climate with fewer temperature differences throughout the year and higher annual precipitation and ultraviolet irradiation (17, 18).”

Comment 20: Line 250: Primacy claim here. Please address as noted above.

Response: According to the editor’s suggestion, we have revised the manuscript as follows.

Page 11, line 641: “Confirmation of our findings are anticipated in other populations, it may be difficult to find subjects living in a large variety of climates maintaining similar living habits.”

Comment 21: Line 264: Not clear what you mean “self controllable”? Perhaps “Self motivated”?

Response: According to the editor’s suggestion, we have revised this sentence as follows.

Page 12, line 713: “It was expected that women who were self-motivated and could input details into the app and those who were sexually active would be more likely to use this app”

Comment 22: Line 274; again, would change to avoid causal language here.

Response: According to the editor’s suggestion, we have revised this sentence as follows.

Page 12, line 732: “Our study found that menstrual cycle length and BBT, both of which were previously considered to be stable, are associated with age and external environment.”

We thank the editor for their helpful and constructive comments on our manuscript.

We feel that the suggestions have helped us to greatly improve our paper, and we hope that the revised manuscript will now be suitable for publication.

Other than the requested changes, we altered documentation to improve readability.

We look forward to hearing from you in due course.

Sincerely,

References:

H, Yoshida; H, Sakamoto; A, Leslie; O, Takahashi; S, Tsuboi; K, Kitamura. Contraception in Japan: Current trends. *Contraception* (2016) 93: 475–477

Editor's comments:

Comment 1: *The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:*

- A. *OPT-IN: Yes, please publish my point-by-point response letter.*
- B. *OPT-OUT: No, please do not publish my point-by-point response letter.*

Response: A. OPT-IN: Yes, please publish my point-by-point response letter.

Comment 2: *As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA. Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.*

Response: We understand and agree to check the eCTA forms.

Comment 3: *Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.*

Response: We have checked our manuscript but did not need to change any terms.

Comment 4: *Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.*

Response: We confirm that our revised manuscript does not exceed 5,500 words.

Comment 5: *Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.*

Response: We confirm that the title conforms to these requirements.

Comment 6: *Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:*

- * All financial support of the study must be acknowledged.*
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.*
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.*
- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).*

Response: We confirm that our acknowledgements include the required information.

Comment 7: *Provide a short title of no more than 45 characters, including spaces, for use as a running foot.*

Response: We confirm that the short titles conforms to these requirements.

Comment 8: *Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."*

Response: We have provided a précis according to the specifications.

Comment 9: *The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.*

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

Response: We confirm that our abstract and manuscript are consistent. The word count of the abstract is 262 words

Comment 10: *Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.*

Response: We confirm that standard abbreviations have been used and have been spelled out at their first use in the abstract and again in the body of the manuscript.

Comment 11: *The commercial name (with the generic name in parentheses) may be used once in the body of the manuscript. Use the generic name at each mention thereafter. Commercial names should not be used in the title, précis, or abstract.*

Response: We confirm that the commercial name has been used only once in the revised manuscript.

Comment 12: *The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.*

Response: We confirm that no virgules have been used.

Comment 13: *In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone. If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts. Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%).*

Response: We confirm that our manuscript complies with these requirements.

Comment 14: *Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here:
http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.*

Response: We confirm that our tables conform to the required style.

Comment 15: *Figures 1 and 2 may be resubmitted with the revision as-is.*

Response: We have changed Figure 2 and resubmitted the revised version.

Comment 16: *Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifaauth.htm>.*

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

Response: We acknowledge this information and will reply promptly to any relevant emails.

Comment 17: *If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:*

- * A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and*
- * A point-by-point response to each of the received comments in this letter.*

Response: We confirm that we have read the Instructions for Authors.

We thank the editors and the reviewers again for their helpful and constructive comments on our manuscript.