Author's response to reviews

Title: Herbal Medicine use in pregnancy: results of a multinational study.

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Author's response to reviews: see over
Dear Dr. Richard Nahin and Mr. James Prozenko;

Thank you for comments that were provided on the submitted manuscript entitled “Complementary and Alternative Medicine use in pregnancy: results of a multinational study”, the title of which has been revised to “Herbal Medicine use in pregnancy: results of a multinational study”. We have carefully considered all points made by the reviewers and Editor and revised the paper accordingly. All changes are highlighted in yellow in the revised manuscript.

We hope that the modifications are satisfactory and that the manuscript can be accepted for publication in the BMC Complementary and Alternative Medicine.

Sincerely,

Deborah A Kennedy

On behalf of all the authors
Reviewer's report:

Major Compulsory Revisions
1. Page 4: The objectives of the study are clear: “to characterize the use of CAM in pregnancy from a multinational perspective” but the authors did not do a sound job of explaining why a multinational perspective was necessary. What are its merits over simply comparing several national studies previously carried out separately?"

Response: Thank you for pointing this out. We have elaborated on the benefits of simultaneous data collecting in multiple countries and how we could reach a broader study population than most prior studies in the background section on page 4.

2. Page 7, second paragraph mentions that Chinese medicine use was not specifically queried. Could this have led to under reporting of herbal medicine use if respondents had used Chinese medicine to for reasons unrelated to specific ailments? Authors may choose to acknowledge this in the Discussion section.

Response: We apologize for this imprecision. We did not name any herbs in specific, therefore underreporting should not be differential between herbal medicine and Chinese medicine in specific. To avoid confusion we have removed this statement. We have added that there may be some under reporting of herbal medicines as herbal names were not specifically asked about as a limitation in the discussion section, page 18.

3. The authors use the term: Determinants of herbal medicine use”. Maybe the more appropriate term would be” Factors significantly associated with Herbal medicine use”, since we are not particularly sure that the factors mentioned are the ones which actually determined herbal medicine use...

Response: We agree. This change has been made on page 12 and Additional file 4.

4. Factors associated with herbal medicine use were identified in the Results section and reiterated in the discussion section but the authors did not attempt to explain or suggest possible reasons for these associations in the Discussion section of their paper

Response: We have revised the paragraph where we discuss our finding on factors associated with herbal medicine use in light of prior studies. We now state in page 17 in the discussion that “Several of the factors associated with herbal medicine user are different from previously reported studies in terms of age and education [13]. However, Forster et al. did find in their study that herbal medicine users were more likely to be nulliparous [26]. These differences from previous studies may simply reflect a more representative user group that we were able to reach via the use of the internet rather than being limited to a specific antenatal clinic or geographical area. We have specifically discussed the possible explanations of our findings on alcohol (page 17), which we found very interesting.

Minor Essential Revisions
1. Line 6 on Background paragraph says “Surveys on the use of herbal medicines in pregnancy have been conducted in Australia, Canada, Italy, Sweden, Norway, United Kingdom, and USA”-
This sounds as if these are the only regions of the world where such surveys have been done. Maybe the authors could also acknowledge that similar surveys have been done in Africa and Asia.

Response: We agree. We have revised the sentence page 3 and now specifically state that our references are from the western world.

2. Page 4 first sentence reads: In general, studies have found that herbal medicine users are women between over the age of 35.....Authors should review this sentence so that it makes grammatical sense.

Response: This has been corrected.

3. First sentence of Methods paragraph reads: This was a multinational, cross-sectional, internet-based study simultaneously performed in several countries worldwide. Was it done worldwide? Two continents: Africa and Asia were not included in the survey. I therefore would not regard the study as a worldwide study.

Response: We agree. Since the study was not worldwide, we now limit this statement to “This was a multinational, cross-sectional, internet-based study”.

4. Page 6, last sentence of first paragraph reads: Conventional medications were coded according to the ATC classification system. What does ATC stand for? Acronyms should be fully explained for the laypersons the first instance they are mentioned. Thereafter they can be used as just acronyms.

Response: Thank you for reminding us about this. ATC stands for Anatomical Therapeutic Chemical (ATC) classification system. We have included this explanation in the manuscript, page 7.

5. A grammar/typo error on page 6, second line of last paragraph: ”When a multi-herbal combination was entered, a internet search”......instead of; an internet search....

Response: Thank you, this has been corrected.

6. Page 7, second paragraph, line 3 says: Other CAM medicines, such as acupuncture, traditional Chinese medicines, were not specifically queries. The word “and” is missing between the words “acupuncture and traditional”. Otherwise the authors can just add “etc” after the word “medicines” to make the sentence grammatically sound.

Response: Thank you, this has been corrected.

7. Page 10, paragraph 2, line 5 reads: highest source was from physicians.....maybe the authors could delete the word “from” just before the word “physicians”

Response: This has been corrected.
8. Page 11 line 17 talks about how Russia has the lowest prevalence of "medication" use. Authors should specify that they are referring to allopathic medication at this point, since Herbal medicines are also a form of medication.

Response: The term allopathic medication has been added.
Reviewer's report 2

2. Minor Revisions

ABSTRACT

Methods: “The secondary aim…..” not “A secondary aim…..”

Response: This has been corrected.

Conclusions,
Line 1: “In this multinational study, ……..
line 3: “Most commonly, ……..

Response: This has been corrected.

DISCUSSION

On page 12, rather than put the name of the herb as follows: “ginger/Zingiber officiale”, it may be better to express it as “ginger (Zingiber officiale)” or “Zingiber officiale (ginger)”.

Response: We have removed the latin names as suggested by reviewer 3 (please see reply to comment no 25).
Reviewer's report 3

Major compulsory revisions
1. Recommend changing the title of the paper to HERB USE in pregnancy since that is the focus of the paper.

Response: This change has been made. The title has been rephrased into “Herbal Medicine use in pregnancy: results of a multinational study”

2. Can the authors explain why they chose to include homeopathy in with “herbs”? Not all homeopathy is herbal and it seems like the focus of the paper is herbal medicine use.

Response: Homeopathy use was not included with herbal medicine use. Separate numbers were originally reported for herbal medicine and homeopathy. The homeopathy results have been removed from this version (please see reply to comment 8).

3. This is a wonderful data set – congratulations on getting such a big sample size’

Response: Thank you.

4. Please not that this is a secondary data base analysis.

Response: Describing herbal medicines use was one of the primary aims of the multinational study. It was therefore not a secondary database analysis. A copy of the actual survey has been provided as confidential to the Editor and Reviewers.

5. Background section
Agree that herbal medicine is top used – rates of homeopathy vary from country to country
Would recommend making 2 sentences to clarify that point

Response: We have omitted homeopathy from the manuscript (see reply to comment 8).

6. Recommend separating you Herb use pregnancy references into region or country for example Specify region of world and the rates eg in Norway rates of herb use in preg are …. Currently you have a list of 10 references some out of date and it is hard for the reader to understand your point that currently herb use rates vary from country to country

Response: This change has been made, page 3. We now state the following: “In the Western world, prevalence estimates of herbal medicine use vary considerably across countries, ranging from 52-58% in Australia and the United Kingdom [7, 8], to 40-48% in Norway and Italy [9, 10] and 6-9% in Canada and the US [11, 12].”

7. Recommend keeping the focus on HERB use – not switching back to CAM

Response: This has now been done throughout the manuscript.
8. Need to have a paragraph or sentence why homeopathy is different from herbal medicine and why do you think it is important that your paper report the prevalence for both. Or choose to take out the data on homeopathy all together.

Response: Thank you for this suggestion. To enhance clarity and focus of the paper on herbal medicine we have chosen to remove the homeopathy results all together.

9. The objective of your study is Herb and Homeopathy NOT CAM – please change first sentence in last paragraph before methods.

Response: We agree. This has now been done. We only refer briefly to CAM in the introduction.

10 looks like you have data on Pregnant and post partum women.

Response: This is correct. The questions however, concerned use of herbal medicines during pregnancy only. We have discussed potential recall bias among post partum women under limitations.

11. Please specify what the primary aim of the study was – was the study designed to collect herbal medicine use or is this a secondary data base analysis?

Response: The survey was specifically designed and aimed to investigating allopathic and herbal medicines in pregnancy. We have now provided the complete questionnaire as confidential to the Editor and Reviewers.

12. Third paragraph – please put verbatim exactly the question the women were asked on the questionnaires for herbs and homeopathy.

Response: The verbatim of the exact question posed to all study participants has now been inserted in the Method section as follows: The question “Did you take any herbal preparations during pregnancy (e.g. ginger, Echinacea, valerian, cranberries)? If yes, please provide the name of all herbal preparations you have taken during pregnancy” was posed to all study participants.

13. DID you ask about other CAM use like acupuncture? If not be careful how you use the term CAM.

Response: We have revised the manuscript and tried to use the term herbal medicines throughout the paper as this was the primary aim of the study. We have now omitted mentioning acupuncture from the paper.

14. Did you ask about non herbal supplements like fish oil and melatonin.

Response: Non herbal supplements were not specifically queried in the survey. However, these were a possible response that the respondents provided in the text entry fields. Non herbal supplements were specifically coded in the dataset and excluded from the current analysis.
15. Did you ask about multivitamins – I see folic acid – was that folic acid alone?

**Response:** Folic acid was specifically asked about as a marker of adherence to national maternity guidelines. Multivitamins were not specifically queried in the survey but were a possible response in the text entry field. Multivitamins were specifically coded in the dataset and excluded from the current analysis of herbal medicines use.

16. What did you do with combination products.

**Response:** Combination products were handled in the same manner as multi-herbal products with the exception that the vitamin or mineral component was not coded. This was described on page 7 of the Methods section, now page 8 as follows: “When a product name representing a multi-herbal combination or combination product was entered, an internet search on the product name was performed and the botanical ingredient(s) coded according to the pre-determined classification list”.

17. All the methods refer to herbal medicine you do not mention questions for homeopathy – please add these.

**Response:** The details regarding the homeopathy related questions were included in the Methods section on page 7. However, in the revised version of the manuscript, homeopathy results have been removed (please see reply 8). Therefore the Method section now does not include details about homeopathy.

18. When you say herbal medicine was coded with a predetermined list – what do you mean was it based on latin name, common name, name of commerce, WHO monograph definition.

**Response:** The pre-determined list was initially compiled by the survey development team (Angela Lupattelli and Hedvig Nordeng), with the primary focus on the common name and the associated latin name. A 7 character specific code was assigned to each botanical following the format of the Anatomical Therapeutic Chemical (ATC) code convention as a means to standardize the coding in the questionnaire database. The following explanatory text has been added to the Methods section, page 7: “The responses to the herbal medicine text field were coded according to a pre-determined classification list of herbs by the national coordinator in each participating country”.

19. What did you do with products that were multivitamins or non botanicals if they were included did the herb have to be >50% of the ingredients by weight ??? or in the top 5 ingredients on the list of ingredients?

**Response:** Multivitamins were specifically coded as E000021 – Supplement, or using the ATC code B03AE02 - Iron and multivitamins, B03AE04 - Iron multivitamin and folic acid or B03AE03 - Iron, multivitamin and minerals, depending on whether the various components could be identified. In many instances women simply provided the description “multivitamin” or “prenatal vitamin” with no specific brand identification. These were not included in the analyses on herbal medicines.
20. If you had a product that had more than one herb – like a tea with chamomile, ginger, and peppermint your methods refer to the “top ingredient” or “order of presentation” on the list which would make it classified as chamomile – This is misleading to the read and does not truly represent the true prevalence as you are not counting second and third etc ingredients. Please add more description of what you did and why you classified them like that – was it teas, tinctures, or tablets. How many single ingredient products?

**Response:** Thank you for drawing our attention to the need for the additional clarification in this area. We now state that “When a product name representing a multi-herbal combination or combination product was entered, an internet search on the product name was performed and the botanical ingredient(s) coded according to the pre-determined classification list. The form of the herbal medicine was not specifically requested (tea, tablet, or tincture)” To use your example, the tea with chamomile, ginger, and peppermint, was coded as chamomile, ginger, and peppermint. So all of the botanicals in a combination were coded. With respect to the “order of presentation”, there were several fields in the survey associated with herbal medicines a text entry field that captured the herbal and a second field that captured the reason for use. A woman may have entered peppermint, ginger in the “herbal medicine” and indigestion, nausea in the “reason for use” field. Here the association would be according to the order of presentation, i.e., peppermint for indigestion and ginger for nausea. This issue has now been clarified in the Method section as follows: When several herbal medicines and reasons for use were provided, the association between the herbal medicine and its use was made according to the order of presentation”.

21 also please list web sites the you found the products – do you just use google or did you look them up on a database?

**Response:** All products were identified using Google as the search engine to identify websites with the ingredients of a product.

22. For homeopathy could they tell you what they used? How do you know if the homeopathy was not herbal based – if it is not herbal based how does it help to present this data.

**Response:** The survey did not specifically ask the respondents for the name(s) of the homeopathic remedy used. Some women did respond with terms that are associated with homeopathic remedies such as Schüssler salts, hepar sulf or arnica. These were classified as homeopathic medicines. Arnica is a toxic botanical and generally not available, as such, over the counter. Since homeopathic medicine names were not specifically requested, when a botanical name was used, which could possibly have been a homeopathic remedy e.g., chamomile, this was classified as a botanical. As this information includes more uncertainty we decided to remove it from the paper (see also reply to comment no. 8).

23. Would recommend the focus of the paper be HERBS not CAM as you did not specifically ask participants about this and it could underestimate the true prevalence.

**Response:** We agree. Herbal medicine has been made the focus of the paper. The title and manuscript text have been revised accordingly.
24. Why did you not do logistic regression for homeopathy users?

**Response:** This was done but not reported due to space limit.

**RESULTS**

25. In your result sections - can you clarify how you know that women were using these specific latin species or are you assuming that they did – did they women write down the species for you in the result sections – there is much variability by country to country of common names

**Response:** In most instances, women reported the name of the herbal medicines which was recoded into specific codes for botanical common name. References to latin binomial names have been removed in the Results section.

26/ Did the women write down their herbs in their own languages and then these were translated into English – did you then make an assumption that if they wrote chamomile that it was german chamomile how do you know if was not roman chamomile? Perhaps you do not want to write the latin in the results section – you can put it in the discussion and say to the best of our knowledge these are the most common species that we think women use – you do know what species they used unless they tell you or you have the ingredient labels that list the species – this is an important part to address. Please do not report the latin name of the plant unless the participants told you.

**Response:** The national coordinators in each country were responsible for coding the women’s herbal medicine responses according to a pre-determine classification list of herbal medicines. This pre-determined classification list of herbal medicines was developed by the survey development team and included the common name, latin name and a code. The coding system that was developed followed the format of the WHO’s ATC classification system, using available codes not assigned to allopathic medications. Additional information has been added to the Methods, page 7.

27. In results – please specify how many combination products you had and how many single herb products.

**Response:** This information has been added to the table in Table 1.

28. Recommend you take out the CAM prevalence this is not the focus of your paper.

**Response:** We agree. This has now been done.

29. Discussion – Please reorganize the first paragraph with your main findings – next follow with the countries prevalence.

**Response:** We have now included the following statement in the first paragraph of the discussion “Three findings are specifically important. Firstly, we found that the use of herbal medicine in pregnancy varied considerable between countries, but that many of the same herbs
are used. Secondly, there were no specific features that characterized the woman who used herbal medicines in pregnancy across all countries. Thirdly, in most countries women relied on informal information sources in their decision to use an herbal medicine in pregnancy.” In the third paragraph we now present the countries prevalence.

30. Again it is fine to say what the latin name of the plant is – just say this is what we think the plant is but it is a limitation of the study. Limitations not listed
Dependent on women to report herb's name - did not ask women to specify the latin name of the plant, did not ask about all ingredients in products, types of products _ teas tinctures (alcohol based) and tablets

Common names of plants are different in different countries
Duration of use of pants and did there use change when they went from pregnant to post partum.

Response: We have incorporated additional limitations into the paper.
Associate Editor's comments:

The authors have presented data on an important topic, use of herbal medicine and homeopathy during pregnancy. The international perspective is unique, as is the large data set. However, as noted by the reviewers, a number of issues need to be addressed before the manuscript is ready for publication. In addition the Associate Editor has identified some additional issues as follows:

1) There are discrepancies between the sample population in the present study (N=9459) and Ref 37 (Hameen-Antilla et al.) (N=7092). Specifically, different broader inclusion criteria were used in the present study. Given these differences, it is inappropriate for the present study to cite Ref 37 as providing evidence that the current study population was similar to the birthing populations in participating countries (table 1 in Ref 37). The authors need to replicate Table 1 (Ref 37) for the present cohort of 9459 women.

There is evidence that individuals participating in Internet surveys are healthier than the general population (e.g. Adams and White, Eur J Public Health, 18(3): 335-338). Since CAM use has been associated with healthy behaviors or a healthy lifestyle in a number of studies, it is suggested that if health behavior data were collected (smoking, alcohol, physical activity levels, diet, etc), that they also be compared to national population data.

Response: Thank you for these comments. We have now deleted reference to Hameen-Antilla et al. and added supplemental material to the paper, namely an extensive table (Additional file 2) summarizing the comparison between the study population characteristics and birthing populations for each country.

Information about smoking behaviors in pregnancy - as proxy of lifestyle – is also outlined in such table and we found it to be comparable across the respondents and participating countries. Data on alcohol consumption was not compared as national statistics on alcohol consumption was not available in most countries. More than one study (Smith et al., Am J Epidemiol. 2007; West et al., Addiction. 2006) has however shown that the population recruited via web-based studies is comparable in age, education and health status to the population recruited via paper-based questionnaires.

2) Please present the number of excluded cases.

Response: This has been done, please see Figure 1.

3) Please describe how missing data were handled ?e.g., individuals excluded from analyses? Imputation?

Response: We have included information on missing data as footnotes in the tables. No variables included in the analyses have missing values for more than 0.5%. There was no imputation performed.

4) Please provide a table listing the various websites where the present survey was posted. The authors state that these websites were ?commonly visited by pregnant or new mothers.? How
was this statement documented? Is information available on the total number of hits for these websites during the study period compared to other websites?

Response: This information has been included in Additional file 1.

5) What systems were in place to identify or prevent individuals from entering data more than once (multiple submissions)?

Response: The survey results were reviewed to ensure that duplicate responses were not recorded. We now state that “Collected data were scrutinized for the presence of potential duplicates (based on reported country of residency, socio-demographic characteristics, date and exact time of questionnaire completion) but none were identified”.

6) In many cases, data is presented for the first time in the Discussion. These data should be moved to the results? e.g., comparison to birthing populations in participant countries (since, as item 1 above, this needs to be new data and not a citation of Ref 37); percent of those accessing survey but declining to participate; time since event data (i.e., time since took the herbal medicine) (e.g., Discussion states that 49.4% of herbal medicine use was more than one year in the past).

Response: Thank you for noting this. The additional information has been added to both the Methods and Results sections. We have also re-organized the Results section and present the herbal medicine variables first and thereafter the socio-demographic variables.

7) Authors must include standard errors or 95% CI whenever they present frequency data (i.e., proportions, percentages). Whenever SE are greater than 50% of the point estimate (e.g., 5%, SE. 2.6%), the data are unreliable and the point estimate cannot be presented. In these cases, the authors may want to group data (e.g., for most frequently used herbal medicines, it is probably the case that a point estimate of 0.1% is unstable? these herbal products could be grouped together; the authors could indicate which herbal products comprised this group)

Response: Standard errors have been calculated for all of the percentages presented. Where the SE > 50%, these results have not been reported and replaced with an “*”

8) Please check the web links for references 1-4. Many do not work as listed (although could be found by searching Internet). Once corrected, for each reference, please state the last time accessed.

Response: All weblinks have been checked and the date of last time accessed added.

9) When they exist, references to documents on the Internet should provide the full reference for the document, not just the title and web link

For instance, the full reference for Ref 3 should be Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007.


**Response:** All references to documents on the Internet are now presented as full references.