Author’s response to reviews

Title: Use of phytoestrogens and effects perceived by postmenopausal women: result of a questionnaire-based survey

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

we thank all referees for their careful revision of our manuscript. Their suggestions, comments and criticisms have all been taken into account in the revised version of the manuscript.

We have refined the analysis according to the referees’ suggestions: in particular, women who declared to be new users have been excluded from the analysis of positive and negative perceptions and the relevant harmonization of presented data has been carried out in Results and Figure 1 on the basis of the duration of the therapy.

In addition, thanks to the referees’ questions, we noticed that some of the questions included in the original Italian version of the questionnaire had inadvertently been omitted in the English translation; thus, we integrated the questionnaire (in the supplementary material) with these 5 questions. Moreover, an additional table (now Table 1) describing characteristics of respondents grouped by duration of therapy is now provided.

Here below is a point-by-point outline of our responses (page numbers refer to the revised version with highlighted changes). Note: Q: Question, A: Answer

Best regards,

Elisabetta Poluzzi
REVIEWER 1 – MAJOR COMMENTS

(Q1) Sixteen percent of respondents reported first-time use of phytoestrogens. Consequently, the questions on positive and negative perceptions of phytoestrogens since beginning use are not applicable to these women, and they should be omitted from analyses of these items.

(A1) Women who declared to buy the phytoestrogen-containing product for the first time (27) have been excluded from the analysis of positive and negative perceptions; please notice revised and highlighted data in second paragraph, page 7. Results obtained from the comparison between short-term and long-term users in terms of positive and negative perceptions (now Table 2 and 3) did not significantly change since they frequently missed the answer to these questions: Results (third paragraph, page 7) and Abstract were updated accordingly.

(Q2) Please provide more detail on how eligible participants were identified and recruited. Was this done by the pharmacists, based on a woman’s purchase of a phytoestrogen product?

(A2) It has been now specified that all women who were buying food supplement containing phytoestrogens were asking to enter the survey. Please, find the revised sentence in first paragraph of the Methods section.

(Q3) The Discussion section states that this study is the first to provide data regarding patterns of phytoestrogen use for postmenopausal symptoms. The authors need to do a more thought literature review, as there have been a number of publications on this topic.

(A3) We now specified “Italian” in the revised version (first line, first paragraph of the Discussion section, page 7).

(Q4) The current study includes only phytoestrogen purchasers, so does not provide information on the percentage of per- or postmenopausal women using phytoestrogens. This needs to be discussed as a limitation.

(A4) Assessing the prevalence of phytoestrogen use in peri- and postmenopausal women represents a very important research topic. However, it was out the scope of the manuscript, since our method cannot provide prevalence estimation because of the absence of a denominator.

(Q5) It would help to have a table summarizing the characteristics of respondents, perhaps comparing subgroups based on a key variable such as length of use, or peri- versus postmenopausal status.

(A5) We prepared a table with the characteristics of recruited women comparing subgroups according to the duration of therapy: new users, short-term users and long-term users: Table 1.

(Q6) Tables 1 and 2 indicate in footnotes that data are missing on relatively large percentages of respondents. Please discuss further, including how nonrespondents differ from respondents, e.g., are they predominantly first-time purchasers.

(A6) Most missing data in Table 2 and 3 (former Table 1 and 2) regarded women who declared to be new users (27). Data presented in these Tables have been modified according to the observation reported in (Q1); please, refer also to (A1).

REVIEWER 1 – MINOR COMMENTS

(Q1) The next-to-last paragraph in the Background section is not quite clear – is the message that phytoestrogen is likely to be under-reported to physicians because it is considered to be a food
supplement? If so, it is unclear why that would hamper assessments of phytoestrogen use in the surveys. This has been done a number of previous surveys. 

(A1) We clarified the message in the revised manuscript, by rephrasing the relevant sentence as follows (page 5, lines 4-5): “Therefore, direct dispensation to the patient by the pharmacists represents the most suitable observational point to collect data on this topic.”

(Q2) Please clarify whether the survey was self-administered but distributed by pharmacists, or administered to respondents by pharmacists.

(A2) It has been now specified that questionnaires have been distributed by pharmacists and autonomously filled-in by women. Please find the revised sentence highlighted in the first paragraph of Methods section, lines 5-7.

(Q3) Numbers and terms are not quite consistent in several places. The abstract specifies 190 post-menopausal women ages 38-77, but the introduction mentions peri- and postmenopausal women, and the first paragraph of results gives the age range as 37-77.

(A3) We have harmonized these figures throughout all manuscript: peri- and postmenopausal women aged 38-77 (Abstract section, page 2 and first line, first paragraph of the Result section page 6).

(Q4) Please indicate how postmenopausal and perimenopausal stages were assessed/defined. There doesn’t seem to be a relevant question included on the survey.

(A4) Peri- and postmenopausal stages have been defined from women’s answers: question included in the Italian original version of the questionnaire, but missing in the English version (Q11 page 2 of the revised questionnaire, “Are you already in the postmenopausal period?”).

(Q5) The sentence regarding 25 products containing phytoestrogens would be better placed in the Methods section.

(A5) The name of the product have been asked at the end of the questionnaire; we added this question in page 4 of the revised version of the questionnaire. Also in the method section, this question has been mentioned as follows: “At the end of the questionnaire, the name of the product was recorded”

(Q6) The discussion section notes that the beneficial effect of phytoestrogens on hot flushes increase with long-term use, while other positive perceptions decreased with long-term use. The authors are using between-woman comparison to make interferences about within-woman changes over time; that limitation should be noted.

(A6) Women have been interviewed only once, so no data on follow-up is available. Our analysis, therefore, showed differences in perceptions between short-term and long-term users, as reported in the Methods section. In the present version, we added a comparison between short- and long-term cohorts on demographic and clinical characteristics. As a matter of fact, no statistically significant differences were found between the two cohorts, except for age and menopausal status (as expected). These data are now included in Table 1.
(Q1) How duration of use was assessed? It was not in the questionnaire. Since their results were base in stratification of duration, it is important to give more details. Please state in the Methods section.

(A1) Question on the duration of the treatment was missing in the English version of the questionnaire, but included in the original Italian version. We updated the questionnaire with question 12 page 2 (“How long have you been taking the phytoestrogen”)

(Q2) How menopause (peri- vs. post) was ascertained including “how long since postmenopause”? It was also not in the questionnaire. Please state in the Methods. Women may suffer from some menopausal symptoms more during peri-menopause. Studies have shown a critical widow of therapeutic opportunity, suggesting that duration of hormone deprivation may affect the beneficial effects of phytoestrogens. Thus, suggest the authors check the data by menopausal status and/or duration since menopause.

(A2) Also question on the peri- and postmenopausal status was included in the original Italian version of the questionnaire, but missing in the English version, We now completed the questionnaire with question 11 page 2 (“Are you already in the postmenopausal period?”).

(Q3) How different the phytoestrogen dosage are of the 25 phytoestrogen-containing supplements? Do they contain mainly isoflavones or some could have lignans only or coumstan? Isoflavones have been studied the most for VMS. Different composition and dosage may affect the participants’ perceptions. Please describe more details about the supplements in the methods or results.

(A3) Thanks to this observation we checked all products’ label and added a sentence regarding the composition of the products in the third paragraph of Results, lines 2-3.

**REVIEWER 2 — MINOR COMMENTS**

Questionnaire:

- Q6: “qualification” is not a proper translation, when this is actually the educational level. The question has been changed as suggested (Q6 page 1)

- Q11: I think “have you ever had..” is what the authors were asking. And it should be “high blood pressure” not “high pressure”. Sentence corrected as suggested (Q15 page 3)

- Q14: “From the beginning of treatment..” – is the timeframe that the authors were really asking? If it is, then I don’t think people would likely report they feel the effects right away.
We rephrased the English version of this question in order to better convey the Italian meaning. In the revised questionnaire, these questions are reported as follows: “After starting the treatment...”.