Author's response to reviews

Title: The effect of physical activity and body mass index on menopausal symptoms: a cross-sectional study in primary care

Authors:

Makbule N Tan (drnesli293@hotmail.com)
Mehtap Kartal (mehtapkartal@gmail.com)
Dilek Guldal (guldal.dilek@gmail.com)

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

We are so thankful for the fruitful comments of the reviewers. We believe that they were so helpful for the improvement of our manuscript.

Below you will find our replies for their recommendations. We tried our best with a statistician consultancy for further statistical analysis recommended. If offered any, we would appreciate for further recommendations.

Sincerely,

Neslisah TAN, MD

Reviewer 1.

Major Compulsory Revisions

My major concern is about the contribution of this study to improve on knowledge. In background section, you cite studies that relate menopausal symptoms with physical activity leading to contrasting results. However the present study does not provide new results respect to some cited studies, with few little exceptions (e. g. smoking status). Furthermore, the relationship between the scores of MRS and IPAQ were previously reported by Canário AC et al. in a similar way to your study (Canário AC et al. The impact of physical activity on menopausal symptoms in middle-aged women. Int J Gynaecol Obstet. 2012 Jul;118(1):34-6 and da Silveira Gonçalves AK et al. [Impact of physical activity on quality of life in middle-aged women: a population based study]. Rev Bras Ginecol Obstet. 2011 Dec;33(12):408-13.). These studies were conducted on Brazilian population and ethical and cultural differences could play an important role in menopausal symptoms, legitimizing the investigation on Turkish population. However, I suggest at least citing these studies and justifying the need of a similar study in Turkish population.

Recommended references are read and the one in English is included as one of the references. As the reviewer pointed out ethincal and cultural differences seem to have an important role in menopausal symptoms. We tried to emphasize it in the background part of the manuscript.

Because IPAQ provides data about sitting time, can you provide results about this item? I suggest including this point in your analysis because, in my knowledge, it has not been related to menopausal symptoms, previously.

“Sitting time” in IPAQ is also provided as the reviewer recommended within the results section.

Because HRT may influence body composition, I suggest to take it into account when you analyze the effect of BMI. Are there differences between inactive and active women respect to confounding factors such us, educational level, employment status, etc...? I recommend you to adjust your analysis for these variables.

As recommended we further analyzed the data for multiple linear regression modeling, however we found that the assumptions of regression analysis (eg. normality assumption, we transformed the independent variable, dependent variable, or both. And we conducted a regression analysis, using the transformed variables and compute the coefficient of determination (R2), based on the transformed variables. But the transformation was not successful.) were not met. When we forced modeling we found that the coefficients of determination (R²) were between 6.5-8.5% for total MRS, and its subscales. We would be so pleased to do if there would be any more recommendations.
Minor essential revisions

Methods, instrumental and data collection

How were weight and height measured? Please, insert name and company of instruments or, indicate if they were simply asked to participants. If the latter is the case, this might explain the lack of relationships between BMI and menopausal symptoms and should be mentioned in discussion.

As we measured the participants’ weight and height with a standardized instrument, (Mewa GmbH/Schwerin-M318800). We add the information related to the instrument in the method part.

Results, second sentence - ‘The MRS total score were also high in non-smoking...’. Change high with higher.

The sentence is corrected as recommended.

Discretionary revisions

Background, second sentence

-Provide reference for: ‘while 75-80% of women...’.

-the use of semicolon make the sentence a bit confusing: can you rephrase?

Concerned reference was in Turkish, so we prefer to refer to an international one and updated the data with this reference. The Turkish reference was replaced by “Prevalence of hot flushes and night sweats around the world: a systematic review”. And the sentence with semicolon is rewritten for better understanding.

Reviewer 2.

General Comments:

The public health implications of this work from a clinical perspective are recognized, that is finding alternative methods to alleviate menopausal symptoms that are not hormone therapy based. However, there is very little new information offered to the literature from this manuscript. In addition to the novelty, there are several major concerns if addressable, would strengthen this manuscript. It is the hope of this reviewer that the authors will receive these comments in the spirit in which they are offered – to improve the reporting of their work.

We worked on the manuscript in line with the reviewers recommendations for major concerns. We hope we managed to address all concerns.

Major Complusory Revisions

1. Novelty: The influence of physical activity (PA)/exercise (EX) and BMI on menopausal symptoms has been investigated for over a decade. Although there are some aspects of the literature that are incompletely characterized, the research design and methodology used in this study will not assist the clarity within this literature.

Genetic, race and cultural differences are known to be effective on the incidence of menopausal symptoms but in this respect there are no regiospecific studies on this topic. Perhaps the conflicting results in the literature may be, not only because of methodological errors or differences but also the differences in reality. The present study thus undertakes to assess the effects of physical activity and BMI on menopausal symptoms in addition to sociodemographic factors influencing menopausal symptoms of Turkish women in Turkey, a country located mostly on Anatolia in Western Asia.
2. Introduction: The introduction did not set up the purpose of the study very well. For example, an introductory sentence could have focused on the issue of symptoms in general before discussing PA effects on symptoms.

As recommended an introductory sentence is added before the discussion of PA effects on menopausal symptoms.

The addition of the citation that PA/EX increased hot flashes is not developed which is critical as it reverse the direction from other content.

It is obvious that the literature has conflicting results, and this point is emphasized.

Finally, there is a well-established relation between PA/EX and BMI with those that are more active having a lower weight status. The potential interaction of PA/EX and BMI on symptoms remains an important consideration. Additionally, PA is not the same as EX and intensity and mode are important considerations regarding their influence on symptoms. Note that the introduction could have also benefited from a hypothesis.

It is true that BMI, PA and menopausal symptoms may have potential interactions. As recommended we further analyzed the data for multiple linear regression modeling, however we found that the assumptions of regression analysis (eg. normality assumption, we transformed the independent variable, dependent variable, or both. And we conducted a regression analysis, using the transformed variables and compute the coefficient of determination ($R^2$), based on the transformed variables. But the transformation was not successful.) were not met. However we forced modeling for interaction, and cannot find any interactions for both total MRS and its subscales so we did not mention within the manuscript.

<table>
<thead>
<tr>
<th></th>
<th>Psychological</th>
<th>somatovegetative</th>
<th>urogenital</th>
<th>Total MRS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta</td>
<td>t</td>
<td>p</td>
<td>Beta</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.028</td>
<td>-0.484</td>
<td>0.629</td>
<td>-0.008</td>
</tr>
<tr>
<td>IPAQ score</td>
<td>-0.220</td>
<td>-3.130</td>
<td>0.002</td>
<td>-0.146</td>
</tr>
<tr>
<td>BMI X IPAQ</td>
<td>-0.095</td>
<td>-1.379</td>
<td>0.169</td>
<td>-0.019</td>
</tr>
<tr>
<td>$F$</td>
<td>3.382</td>
<td></td>
<td></td>
<td>1.861</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.023</td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
</tbody>
</table>

3. Statistical Analysis:

The first concern is sample size. Although the sample size is robust, how was this study powered? Were there different enrollment targets for the peri-menopausal vs. the postmenopausal groups?

The study was planned mainly to show the effect of PA and BMI on menopausal symptoms. The power of the study to show the association between PA and total MRS scores is calculated as 100% and the association between BMI and total MRS scores is calculated as 96%. There are no enrollment targets for the peri-menopausal vs. the postmenopausal groups. These groups are just for the determination of the appropriate participants for the study and description of the study population.

The second concern is more important albeit it can be addressed as it relates to the statistical analyses. For the primary outcomes of interest, BMI and PA/EX, the authors manipulated continuous variables into a categorical variable which is often acceptable as a secondary analysis but not as a primary and sole analysis.

The reviewer’s comment is accepted as reasonable and irrefutable. For correlation analysis they are used as continuous variables.
The use of linear regression techniques would a) aid the interpretation of the data, b) allow the exploration of an interaction effect (e.g. BMI and PA) on the symptoms of interest, and c) allow for control of important covariates such as age or menopausal status.

As recommended we further analyzed the data for multiple linear regression modelling, however we found that the assumptions of regression analysis (e.g. normality assumption, we transformed the independent variable, dependent variable, or both. And we conducted a regression analysis, using the transformed variables and compute the coefficient of determination ($R^2$), based on the transformed variables. But the transformation was not successful.) were not met. When we forced modelling we found that the coefficients of determination ($R^2$) were between 6.5-8.5% for total MRS, and its subscales. We would be so pleased to do if there would be any more recommendations.

The final concern is related to the expression of results in the text. For example, numerous times throughout the text it appears that linear regression or correlational analyses was used (which is not described in the statistical methods) with the use of expressions such as: “No significant relationships ($p>0.05$) were observed between BMI and all MRS subscales...”. If this is the case, the statistics section needs to be amended and the writing needs to be changed to reflect the strength of the association with the addition of an r value.

Correlational analysis are included within the manuscript as recommended as Table 3.

4. Co-morbidities. The handling of the chronic conditions requires additional explanation and likely analyses as some key conditions would influence menopausal symptoms differentially. For example, depression would likely influence psychological outcomes and osteoarthritis would influence reports of joint discomfort.

It is true that co-morbidities can effect menopausal symptoms, however the number of cases as depression (14 participants), and musculoskeletal disorders including osteoarthritis (6 participants). This limitation avoids us to mention about these in detail.

5. Discussion.

The discussion could benefit from

1) a strong introductory paragraph stating the novel findings of the study,

2) a reduction in the content discussing cultural and eastern/western implications for descriptive data as this was not the focus of the study,

There are some discrepancies between the reviewers especially about the cultural aspect of the study. So we prefer to reply the concerns of first reviewer about the cultural differences and add the recommended references and did not change the scope of the introductory part of the discussion.

3) an increased focus discussion regarding the primary independent variables of interest for this study of PA/EX and BMI,

As recommended we tried to increase the discussion focusing on PA/EX. However as we did have limited significant results about the relation of BMI and menopausal symptoms, we could not have additional concerns.

4) and an integrated discussion regarding the potential interactive effects of numerous outcomes on symptoms including not just PA/EX and BMI but also key demographic outcomes.

As recommended we tried to integrate the key demographic outcomes of the study in the discussion.
Minor Essential Revisions

1. Page 7. Although it is intuitive that greater severity of symptoms adversely influences quality of life, the MRS does not assess this construct. Suggest revising this sentence.

In MRS homepage it is stated that (http://www.menopause-rating-scale.info/objectives.htm): The scale was designed to measure health-related quality of life (QoL) or severity of complaints in aging women. There is a strikingly good association between the subscales of SF-36 and the MRS and the MRS could serve as an adequate diagnostic instrument for menopausal QoL.


2. Page 7. The information regarding “the three levels of PA being proposed at the end” is confusing and not appropriate statistically (forced categorical data). See Statistical Analysis section above.

PA was categorized in three levels as it is in IPAQ: Low, moderate and high.

3. Page 8. A person cannot be overweight and obese. Revise to indicate OR.

The mistake is corrected.

4. Page 9. The formatting of the subheadings within the result section is not consistent.

The subheadings within the result section have been removed.

5. Page 9 and 10. The data regarding the MRS scores and IPAQ energy expenditure should be reflected in a table. Importantly, a descriptive table expressing data from all participants would benefit the reader.

Table 1 and 2 are added including not only the frequencies of the variable but also the means and standard deviations of MRS scores and IPAQ values of the participants as recommended.

6. Page 10. It is misleading to indicate that 94% of individuals who experience depressive symptoms had a BMI > 25 when 91% of the sample had a BMI > 25.

As recommended to avoid any misunderstanding the concerned results are reworded as “A significant increasing trend in the rate of depressive mood was observed from normal through overweight to obese participants”.

7. Page 23. “History of drug use” label on the table should be corrected to reflect estrogen use.

“History of drug use” is corrected reflecting HRT usage.