Author's response to reviews

Title: Associations between body composition and lifestyle factors with bone mineral density according to time since menopause in women from Southern Brazil: a cross-sectional study

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Author's response to reviews: see over
To the Editorial Board  
*BMC Endocrine Disorders*

Dear Editors,

We have just uploaded a manuscript entitled “*Associations between body composition and lifestyle factors with bone mineral density according to time since menopause in women from Southern Brazil: a cross-sectional study*,” which we would like you to consider for publication in *BMC Endocrine Disorders*. The article has been previously evaluated by *BMC Endocrine Disorders* and it was suggested we send a new manuscript, addressing all concerns reported by the reviewers. In the revised manuscript all changes are written in blue.

A detailed point-by-point response to the reviewers’ comments is presented below.

This study examines variables associated with low bone mass, a common endocrine condition that affects climacteric and older women and increases the fracture risk. The present work is especially relevant because enrolled postmenopausal volunteers that were apparently healthy women.

Our group has studied menopause-related disorders since 2000, and has recently published a population-based study regarding physical activity and dietary choices contributing toward a more favorable cardiovascular profile in postmenopausal women. Therefore, this cross-sectional study has served to complement and expand some of our previous findings.

The authors have no conflicts of interest to declare. All have read and approved the final version.

We look forward to hearing from you regarding the status of our paper. Feel free to contact us if you require any additional information.

Sincerely,

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Responses to Reviewers
Reviewer: Lisa Langsetmo
“The aim of this study was to investigate the association of dietary pattern and habitual physical activity with BMD and the influence of body composition, age and time since menopause on BMD in postmenopausal women with no clinical evidence of disease”
The authors conducted a small cross-sectional study (n=100) in post-menopausal women. Results are stratified by time since menopause (<5 yr >= 5 yr). It is well-known women lose BMD after peak bone mass women and that the period surrounding menopause is a period of especially high bone loss. Thus, the highlighted results concerning association between age, menopausal status and BMD are not especially novel, moreover, due to the cross-sectional design the association noted will not reflect the true association with bone loss during this period of increased bone loss. The authors also note an association between BMI, lean mass, DHEAS, and RMR, with BMD after “adjusting” for age and time since menopause. The simple associations probably warrant a more thorough investigation, attending to the fact that these variables are known to be strongly related (and probably linked by multiple causal mechanisms) and hence the appropriate statistical analysis should be used. The authors present both dietary variables and physical activity variables, but the relationship of these variables to BMD is not described in the results or tables, but some mention appears in the abstract. In summary, the main aim of the study does not seem to be adequately described and presented in the manuscript.

Major compulsory revisions:
1. Results should match objectives.
A deep reanalysis of data was done and in consequence, a new version of Results section is presented. In particular, Table 2 shows the relationships between studied variables and BMD in each site.

2. Discussion of results should be put in context of existing literature.
The Discussion was rewritten in order to address this issue. Nine new references were added to the manuscript.

3. Descriptive tables should be included when they are relevant to exposure/outcome
Tables were updated according to the new analysis

Reviewer: Elsa Strotmeyer
General comments to the authors:
The association of lifestyle factors and BMD in women recently experiencing the menopausal transition is an important topic, given that women have a faster rate of bone loss during this time period of their life. However several concerns exist for the study, as outlined below. Importantly, the stated aims of the study are not fully described in the results and discussion.
1. Is the question posed original, important and well defined?
- This is an important research question with a major public health impact. A better understanding of risk factors associated with BMD could provide targets for prevention in women immediately after menopause and may reduce the number of fractures after menopause.
- Although the research question is well defined and important, it is not an original one since many of the risk factors of interest are already known to affect the BMD. Specifically, key manuscripts from other studies such as the Study of Osteoporotic Fractures, the Study of Women’s Health across the Nation (SWAN), and the Women’s Health Initiative (WHI) have already examined the association between these factors and BMD. These studies need to be appropriately cited and described in the background and discussion.

For example, some previous studies have looked at the effect of:
- Nutrition on BMD [1]
- Physical Activity on BMD [2]
- Body Composition on BMD [3]
- Time since menopause on BMD [4].

- The rationale behind conducting this study is not clear. Was it to see if such risk factors apply to the Brazilian postmenopausal women? The new findings from the results of this manuscript are not clear.

The whole manuscript was revised and data was reanalyzed. The Discussion section was also revised and the four references suggested by the Reviewer were added to the text. Few data are available from the literature regarding the influence of body composition, diet and habitual physical activity on BMD in Brazilian postmenopausal women and this aspect was underlined in the present version of the manuscript.

2. Are the data sound and well controlled?
- Authors excluded smokers as well as participants with diabetes and heart diseases although the rationale for excluding these populations is not clear since other conditions result in secondary osteoporosis and are important to consider. Information about other co-morbidities could have been collected using a questionnaire and adjusted for in analyses rather than excluding populations with disease. The population is highly selective since smoking, diabetes and heart disease are very common in postmenopausal women. These criteria were chosen because of the interest to study women with no clinically established systemic diseases. This information was added to the Methods.

- Although it was mentioned in the introduction that estradiol is the best predictor of fracture, it was not adjusted for in the model. Participants presented low and similar estradiol levels among groups of ≤ or > 5 years since menopause, as expected for postmenopausal women. Probably for this reason preliminary analysis showed endogenous estrogens did not influence on results.

Information about other medications affecting the risk factors or the BMD outcome should have been collected using a medication inventory. Forty participants were on antihypertensive drugs, two women were on statins, and one was taking aspirin. A sentence was added to Results addressing this point.

- The definition of “low bone mass” for the regression analyses is unclear. How was the variable created and what/why were the cutpoints chosen? Normal bone mass was defined as a T score above -1 standard deviations (SD) and low bone mass was defined as the presence of at least one site of osteopenia or osteoporosis, according to the World Health Organization (WHO). This information was added to the Methods.
- In the logistic regression, authors appear to have adjusted only for the time since menopause. To determine whether or not the risk factors (BMI, lean mass, PA, protein intake, HT) are independent risk factors for low BMD, more variables should have been adjusted for such as history of fractures, family history of osteoporosis, alcohol intake, steroid intake, etc. Also, other medical conditions affecting BMD (2nd osteoporosis) could have been included in the model. Instead of having a separate model for each variable, a possibility is to include all variables in one model.

Logistic regression analysis was adjusted for time since menopause and previous hormonal therapy. The sample size is a limitation to include all variables in one model. A paragraph regarding limitations of the study was rewritten in the Discussion section, addressing this point.

- The risk factor variables are poorly described and many are not adequately included in the results section. The selection of cutoffs for lean mass, mean steps/day, protein intake, and BMI was not justified. The cutpoint variables were not described in the Univariate analyses shown in the Tables. The distributions of risk factor variables are not clear either. For example, how did the cutoff of mean steps/day relate to the distribution of the data in the population? Alternatively, instead of categorizing the continuous variables, authors could have looked at these variables as continuous ones. Furthermore, the BMI cutoff that was used is 25 kg/m2 and was considered as low BMI. This is not a low BMI but normal BMI. Currently, there are better methods to assess low muscle mass by using DXA instead of BIA and this should be listed as a limitation in the discussion section. The variable ‘skin color’ is not defined in the methods.

Results section was rewritten and Tables were updated according to new analysis, in order to clarify the issues pointed out by the Reviewer. Cutoffs of risk factor variables were described in the footnote of Table 3. Lean and fat mass values are now presented by using DXA. Cut point of mean steps by day and categorization in active or sedentary were > or \(\leq\) 6,000 steps per day, according to previous reports. Skin color was obtained by auto-reference. These information were added to Methods section.

3. Is the interpretation (discussion and conclusion) well balanced and supported by the data?
- The results emphasized did not include the study’s strengths and it was not clear what the study added to the existing literature. Key references were missing, similar to the background. Data were reanalyzed and Discussion and conclusion were rewritten, addressing these points. Eight new references were added to the text, including the four references suggested by the Reviewer.

- 19 out of the 119 participants (16%) were excluded. This is considered to be a moderate enrollment rate and could affect the external validity of the study and should be listed as a limitation.

This information was added to the Discussion section, as requested.

- Furthermore, the age range of participants was restricted between 45 and 65 so follow-up after menopause was relatively short. Although the purpose may have been to study this early post-menopausal period, this might have contributed to the null results and this limitation should be noted as well.
Indeed, the purpose of this age range was to study relatively recent postmenopausal women. The present results express the clinical conditions at this period, which is relevant to primary and secondary prevention, and should not be considered as a limitation.

- Conclusions based on the results were incomplete since they did not emphasize the unique strengths of the study. Conclusions were rewritten according to new results.

4. Are the methods appropriate and well described, and are sufficient details provided to allow others to evaluate and/or replicate the work?
- Good detailed description of how the data was collected, including the interassay coefficient of variations.
- More information could have been provided on how the T-score was calculated. Which standard/reference population was used? Young Caucasian women? T-score was calculated based in Caucasian women 20-40 years.
- Also, the dependent variable was not well defined. Although authors talk about bone mass assessment, they were not clear on how was the outcome (low bone mass) classified. Was a T-score<-1 considered to be low bone mass? Low bone mass was defined as the presence of at least one site with a T score < -1 standard deviations (SD), according to the World Health Organization (WHO) This information was added to the Methods.
- For the body composition assessment, the reference for the manufacturer’s formula should be included. Furthermore, it is important to note that it has been shown that BIA is not always very accurate especially in older participants with high BMI. How was the 23.1 Kg cutoff selected? Data about body composition are now presented by using DXA. Methods section was rewritten with information about the method.
- Are any foods from the Brazilian table of Food Composition excluded from the USDA database and if so, would these affect the vitamin D, E or A calculations? These indices need to be better described. In the present version, no differences were found in macro and micronutrients among the groups. Only vitamin A presented a difference in the borderline significance, and in this case foods containing vitamin A are present in both tables of Food composition.

5. What are the strengths and weaknesses of the methods?
- Like previously mentioned, there are published longitudinal studies looking at risk factors associated with low BMD so the unique aspects of the current study are not clear.
- Sample size calculations were done only to detect a correlation of 0.3 between BMD and lean mass only. What about the other variables? Also, stratification by time since menopause in the descriptive data tables may have lowered statistical power. Looking at the independent variables as continuous variables may be an option to consider if the usage of the cutoffs is not well justified. The cutoffs were not included in the descriptive data tables.
Few studies are available regarding lifestyle associated-risk factors on bone mass in women from South America/Brazil. Data were reanalyzed according to suggestions of reviewers.

6. Can the writing, organization, tables and figures be improved?
- The results of the abstract should not be taken directly from the results section, but should succinctly summarize the results.
- Tables of descriptive data should include variables that are in the regression analyses.

Abstract, Results and Tables were updated after the reanalysis of data.

References