Author's response to reviews

Title: Lean Body Mass: The Development and Validation of Prediction Equations In Healthy Adults

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

Re: MS: 9217072930643176: Lean Body Mass: The Development and Validation of Prediction Equations

We would like to thank the reviewers for their feedback. We have taken into account this feedback and have attempted to further improve the paper by addressing these comments as discussed here.

Thank you.

Yours Sincerely,

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Solomon Yu
Corresponding Author
Response to Reviewer 1 (Heliodoro Aleman-Mateo):

Issue 1: ……However, the validation procedures is still confusing for me.

Response/Action: The following was added under the section of study cohort (page 6) to clarify the use of different cohorts for this study:

“CASA was used to derive the PEs for LBM which included anthropometric and biochemistry variables. The selected LBM PEs were then validated in a second independent cohort, the VC (n=52). As sarcopenia is more prevalent in older populations, validation of the best performing PE and other published FFM PEs (Heitmann, Janmahasatian and Deurenberg equations) were then undertaken in the larger population representative NWAHS and FAMAS cohorts (n=2287, age ≥ 50 years).”

Issue 2: In Table 1, the authors present the Concordance R (95% CI), I guess that it came from therestults of the analysis of the concordance correlation coefficient proposed by LinL.

Response: The widely accepted statistical strategies for comparing different methods of measurement of the same variable are to undertake a regression analysis AND to assess agreement using Bland-Altman analysis. For the former an appropriate regression technique is that of Lin as used here and described as follows (MedCalc):

“The concordance correlation coefficient $\rho_c$ (Lin, 1989 & 2000) evaluates the degree to which pairs of observations fall on the 45° line through the origin. It contains a measurement of precision $\rho$ and accuracy $C_b$:

$$\rho_c = \rho C_b$$

where

• $\rho$ is the Pearson correlation coefficient, which measures how far each observation deviates from the best-fit line, and is a measure of precision, and
• $C_b$ is a bias correction factor that measures how far the best-fit line deviates from the 45° line through the origin, and is a measure of accuracy. “

In other words, it is a measure of how much the data deviate from the line of identity which represents congruence between the methods.

The most widely accepted method for assessment of agreement between methods is the method Bland and Altman (B&A) also used here as described in Medcalc:

“The Bland-Altman plot (Bland & Altman, 1986 and 1999), or difference plot, is a graphical method to compare two measurements techniques. In this graphical method the differences (or alternatively the ratios) between the two techniques are plotted against the averages of the two techniques. Alternatively (Krouwer, 2008) the differences can be plotted against one of the two methods, if this method is a reference or "gold standard" method.
Horizontal lines are drawn at the mean difference, and at the limits of agreement, which are defined as the mean difference plus and minus 1.96 times the standard deviation of the differences. If the differences within mean ± 1.96 SD are not clinically important, the two methods may be used interchangeably.

A quick Pubmed survey of the many papers describing methods for the assessment of body composition will show the widespread use of these approaches. Consequently we provided in Table 1 the outcomes of using these statistical approaches when comparing the predicted data, i.e. from using the new equations, PE1-4, with the reference data from DXA. In addition for completeness, we included the usual measures of goodness of fit: RMSE, Pearson’s r and the associated P value.

**Action:** The following paragraph was added to in the manuscript to help clarify this point.

“To assess the accuracy and predictive performance of the prediction equations against LBM\textsubscript{DXA}, a regression analysis as proposed by Lin [29] was undertaken and the concordance correlation coefficient (\(\rho_c\)) was derived. \(\rho_c\) measures how much the data deviates from the line of identity representing congruence between the methods. It is a product of Pearson correlation (\(\rho\)) and bias correction factor (\(C_b\)): \(\rho_c = \rho \ C_b\)\[30\].

In addition, to assess the level of agreement between the two methods, Bland-Altman analysis was performed to obtain the 95% limits of agreement [31]. Furthermore, the goodness of fit with root mean square error (RMSE) and bias (mean error [ME]) was also determined. RMSE and ME were calculated according to the method of Sheiner and Beal [32].”

**Issue 3:** LBM PE1 and PE2 had a values below 0.90 indicating a weak strength.

**Response/Action:** Values of around 0.9 are not considered indications of “weak” association. Bland (of Bland and Altman fame) in the statistical guidance for authors to the British Medical Journal states

“’If we wish to label the strength of the association, for absolute values of r, 0-0.19 is regarded as very weak, 0.2-0.39 as weak, 0.40-0.59 as moderate, 0.6-0.79 as strong and 0.8-1 as very strong correlation.’”

On this basis, the correlations that we found are classed as very strong. Also measures of association of this magnitude are widely accepted in this field as being of high practical significance and use.

**Issue 4:** Is not clear if the authors tested accuracy of the new equation by obtaining the concordance correlation bias. From my point of view this is the most important issue that is not clear how exactly the authors tested accuracy of new equations.

**Response/Action:** The accuracy of the new prediction equations was assessed in the conventional manner statistically as described above and by cross-validation in a
separate population data set – again the most commonly applied strategy. The concordance bias value is not typically provided in papers; a convention that we followed. It can, however, be readily calculated from the data provided using the equation described above: \( \rho_c = \rho c_b \), where \( \rho \) is the Pearson correlation coefficient and \( c_b \) is a bias correction factor.

If the reviewer is actually referring to the measurement bias, i.e. the mean difference between methods, this is provided in column 2 of the Tables.

We have included the results of the bias correction factor in column 5 of all tables so as to not increase the width of the tables.

**Issue 5: If you look the table 2, 3 and 4 this information is missing.**

**Response/Action:** Has been added as discussed.

**Issue 6:** Additionally, a graph of the concordance correlation between estimated LBM by DXA and LBM estimate by the new equation must be included.

**Response/Action:** This would add substantially to the length of the paper since such graphs would need to be provided for ALL comparisons. Furthermore, all salient data of such graphs are presented as the bias and limits of agreement in the Tables. As previously, by convention, where multiple B&A plots would be required, the summary data (bias and limits) are provided in tabular form for brevity.

**Issue 7:** Finally, I would like to see the averaged difference between methods by bland and altman analysis.

**Response/Action:** This value, the bias, is identical to the mean difference, already provided in column 2 in the tables.
In response to comment by the reviewer that the manuscript requires editing, we have also made the following revision to the manuscript:

Abstract

• Conclusions:

The sentence “….This PE may have clinical utility and may help improve the safety of medication use but further studies are required to confirm this.” is replaced by “….Further research is required to determine the clinical utility and if it will improve the safety of medication use.”

Background Section:

• Second paragraph (new and includes previous paragraph 4):

“A major impediment to the routine clinical use of LBM is the reliance on relatively inaccessible or expensive methods of body composition measurements. Computed tomography (CT)…”

• Previous second paragraph is now third paragraph but revised to make it clearer as below:

“Total body weight consists of fat mass and fat free mass. Fat free mass (FFM) consists of bone, muscle, vital organs and extracellular fluid. LBM differs from FFM in that lipid in cellular membranes are included in LBM but this accounts for only a small fraction of total body weight (up to 3% in men and 5% in women) [12]. In the literature, bone mass has at times been included in LBM and at other times not included [4, 13].”

• Paragraph 4: Sentences have been modified as below:

Correction 1: “Anthropometric-based prediction equations (PEs) have been examined as an alternative in measuring LBM in settings where access to these accurate methods is limited.”

Correction 2: In defining the FFM and LBM, the authors in that study proposed that FFM and LBM could be used interchangeably.

Correction 3: The paragraph below was rearranged so it flows better.

“The three PEs were the Heitmann, Janmahasatian and Deurenberg equations as shown below:

Heitmann equation [15]:"
Body fat (kg)_{male} = (0.988 \times \text{BMI}) + (0.242 \times \text{weight}) + (0.094 \times \text{age}) - 30.180

Body fat (kg)_{female} = (0.988 \times \text{BMI}) + (0.344 \times \text{weight}) + (0.094 \times \text{age}) - 30.180.

*Janmahasatian equation*[12]:

FFM (kg)_{female} = (9270 \times \text{weight}) / (8780 + (244 \times \text{BMI})

FFM (kg)_{male} = (9270 \times \text{weight}) / (6680 + (216 \times \text{BMI})

*Deurenberg equation*[16]:

Body fat (%) = (1.2 \times \text{BMI}) + (0.23 \times \text{Age}) - (10.8 \times \text{Sex}) - 5.4

Male = 1, Female = 0

For two of the PEs (Heitmann and Deurenberg equations), FFM was calculated by subtracting fat mass from total body mass. In defining the FFM and LBM, the authors in that study proposed that FFM and LBM could be used interchangeably. Mitchell et al reported that FFM as estimated by Deurenberg equation had the smallest mean difference and overestimated FFM_{DXA} for overweight men but underestimated FFM_{DXA} for all other body mass index (BMI) subgroups [14]. The Heitmann and Janmahasatian equations, on the other hand, overestimated FFM_{DXA} across various BMI categories [14].”

**Results**

- **Paragraph 1 (page 13)**

*Correction 1*: Table 2 compares the performance of various PEs including PE\textsubscript{1} against LBM\textsubscript{DXA} in the total combined NWAHS and FAMAS cohorts as well as in the two gender groups, men and women.

- **Paragraph 2 (page 13)**

*Correction 1*: Table 3 compares the performance of the various PEs across age groups (60-64, 65-79, ≥80).

*Correction 2*: PE\textsubscript{1} consistently over-estimated LBM\textsubscript{DXA} across the age groups but performed better (lowest ME, RMSE values and higher concordance correlation coefficient) than the Janmahasatian and Heitmann equations.

**Discussion**

- **Paragraph 1 (page 15)**

*Corrections 1*: It was hypothesized that the addition of biochemistry variables would result in an improvement in the performance of the PEs and this was seen.
Corrections2: However, the improvement was marginal and insufficient to justify the additional costs.

- **Paragraph 2 (page 15)**
  
  Corrections 1: A significant finding from this study was the development of a new anthropometric PE (PE\textsubscript{1}) for LBM: \( LBM = 22.932326 + 0.684668 \text{ (weight)} - 1.137156 \text{ (BMI)} - 0.009213 \text{ (age)} + 9.940015 \text{ (if male)} \). The close approximation to \( LBM_{\text{DXA}} \) generated by this equation was reflected by its small bias (ME=0.74kg) and precision (RMSE=3.73kg).

- **Paragraph 3 (page 15)**
  
  Corrections 1: Interestingly, the Deurenberg equation appeared to have less bias with a ME of 0.02 kg but similar precision with a RMSE of 3.95 when compared to the newly developed PE.

  Corrections 2: The newly developed PE\textsubscript{1} appeared to have better precision (smaller RMSE) and less bias (lower ME) than the Deurenberg equation only in women and in obese older individuals. In clinical settings where the dose normalization to LBM is required, an overestimation of LBM could potentially lead to higher incidence of dose limiting toxicity. Sarcopenia was an important predictor of toxicity in women with metastatic cancer and colon cancer receiving chemotherapy [8, 10]. It was suggested that chemotherapy dose normalization to LBM may reduce the excess toxicity in women. PE\textsubscript{1} in our study potentially offers a more accurate estimation of LBM over Deurenberg equation in women and obese individual and may have clinical utility in these two patient population groups.

**Tables legends**

The following changes were made to the table legends:

Table 1. Validation of PE LBM in healthy adults from the Cytokine, Adiposity, Sarcopenia and Ageing (CASA) study cohort (n=195) against DXA derived LBM in the validation cohort (n=52).

Table 2. Performance of the CASA (\( LBM_{\text{PE1}} \)) and previously published FFM prediction equations in the NWAHS and FAMAS cohorts (age 50 years and over) in the combined cohort and by gender.

Table 3: Performance of the CASA (\( LBM_{\text{PE1}} \)) and previously published FFM prediction equations in the NWAHS and FAMAS cohorts (age 50 years and over) across various age groupings.
Table 4: Performance of the CASA ($LBM_{PE1}$) and previously published FFM prediction equations in the NWAHS and FAMAS cohorts (age 50 years and over) across various body mass index groupings.