University of Washington

Dear Dr. Warren Ladiges,

Thank you for waiting for the revision of our manuscript and for comment of Reviewer A and B. We had good chance to consider deeply about BMI which is not only for the index of obese but also others. We have revised followed by Reviewer’s comments and the each revised content is described with red letter at the each comment of Reviewer A and B as follows;

Reviewer A:
Introduction is disjointed and did not follow a logical flow or contain
necessary background information. This section could benefit from a more
thorough overview of how BDNF is relevant, including previous work on how
this correlates with BMI from individuals outside of this research group.
Please elaborate on the choice to quantify BDNF and the justification for
investigating the correlation with BMI, medicines, grip strength, etc.
o Furthermore, include works regarding the relationship between BDNF and
medications, frailty, grip strength, etc as these relationships are
investigated here with no mention to relevant findings within the
geroscience field.

Answer: We revised Introduction as the suggestion of Reviewer A *(p3, l2 - 33*). The works regarding the relationship between BDNF and medications, frailty or grip strength, etc were moved to the Introduction from the Result section written in the first paragraph *(p3, l34 – p4, l15, with black letter).*

Methodology requires additional information throughout.
o Correlations with prescribed medicines were mentioned in the statistical
analysis section and discussion, but not in the introduction or methods.
Were participants given a questionnaire? Please describe this in the
methods.

Answer: We described in the Method section that we investigated the prescribed medicines and experienced disease with a questionnaire to participants *(p4 l24 –27)*.

o What was the order of testing? If blood draws were performed prior to grip
strength testing, or vice versa, how could that affect the results?
Answer: We described in the Method section that the blood draws were performed at the end of health examinations *(p5, l14 – 15)* and measured hand grip strength before the blood withdrawn *(p5, l8 - 9)*.

 o For handgrip strength, did individuals get one test? An average of
multiple? What were the instructions given to participants?
Answer: We described in the Method section that the handgrip strength was measured once in each hand and taken the higher value *(p5, l8 – 11).*
o For BDNF, how were samples collected?
Answer: We described in the Method that serum collection is by centrifugation and the measurement of BDNF is by the ELISA followed manufacturer’s protocol *(p5, l14 – 20)*.
Figures are illegible. There is no discernable labeling of the y axis values
in Figure 1.
Graphical representations of correlations would strengthen the manuscript
greatly.

Answer: All figures were re-written clearly with labeling x and y axis and supplemented Figure 2.

Bar graphs do not represent correlational statistics accurately.
Statistical methodology requires expansion and revision. A description of
how correlations were conducted is required. Please report statistics for
all comparisons described, even if not significant. Also, p values alone are
insufficient; please include F statistics, T values, etc where appropriate.
Lastly, serial t-tests investigating individual differences between two
groups must be statistically justified – please report parents ANOVAs
prior to post hoc analyses or describe & justify preplanned analyses.

Answer: We described the statistical analysis that Student t-test is employed only comparison of handgrip strength between in male and female and ANOVA is employed to compare BDNF levels or hand grip strengths across BMI or %BFM categories *(p5, l23 - 25)*. Further, the multiple comparison was made with Bonferroni’s correction *(p5, l26 - 28)*. Concerning to F statistics, I put Levene’s F value and p value in the each Figure legend.

We did not use a regression analysis, therefore we delate the expression of phrase “the relationship between A and B” or “the correlation between A and B” etc.
The discussion section contains a lot of data and descriptive statistics
that should be moved to the results section (potentially via tables rather
than text). Furthermore, the discussion is lacking interpretation of the
data and discussion of the implications of these findings.

Answer: Most of data and statistics are delated from discussion section and some moved to the result section *(p6, l8 - 10).*

We have discussed about the interpretation of the data and described our implication based on BMI is not only for the index of obese but also others, difference from %BFM *(p10, l31 - p11, l6, p11, l4 - 20, p12, l30 - 36).*

Title requires grammatical revision and does not accurately portray the data
presented here.

Answer: Title was changed as expressing the data.
The discussion section focuses primarily on variables other than BMI & BDNF,
which are the emphasized factors discussed in the title, introduction and
conclusion sections.

Answer: We focused on the BMI and BDNF with frailty in the introduction and discussion section. We add in the conclusion section that the thin category with findings of low BDNF levels and weak hand grip strength is “prodromal frailty”.
A discussion on the limitations of BMI is warranted.

Answer: We placed a limitation of the study including BMI at the last paragraph of discussion section *(p12, l22 – 36)*.
Several places throughout the manuscript do not have citations to support
claims made. For example, within the introduction “With aging, individuals
experience reduced appetite and decreased bioavailability of absorbed
proteins” warrants a citation.
Some citations are improperly formatted (for example, first sentence of
methods section “Participants” and first sentence of methods section
“Measurement of serum BDNF concentrations”, etc).

Answer: The citations are properly changed and the phrase concerning appetite decreasing in elderly people was omitted.
Rather than typing all of the percentages of people within each group, a
descriptive table of body fat percentage distribution would be easier to
follow.

Answer: We newly supplemented table 1 and 2 for the % distribution of individualsin the classified BMI and %BFM.
**------------------------------------------------------**Reviewer B:
This manuscript is attempting to explore the relationship between serum BDNF
and BMI on frailty according to physical and psychiatric health in elderly
people. By comparing and analyzing the data, this research illustrates well
about the possible correlation of these two indices among different groups.
Conclusions are correct and well inferred in the results and discussion. In
my view, this manuscript is worth to accept in this journal, however,
several places should be revised before acceptance. First, although each
title of results is well summary the main finding, portion conclusion still
should be provided after the result data showing.

Answer: We put brief conclusion at each result.

 Second, the line over each
bar in figure 1 should be illustrated clearly of the meaning in the figure
legend.

Answer: All figures are re-written clearly.

Finally, we are highly recommended that the conclusion or discussion
with data not shown could be elucidated by elaborate data in order to well
support for the conclusion.

Answer: We re-written introduction, discussion and conclusion with focusing on the BMI and BDNF with frailty *(p3, l2 – 22, p10, l20 – p11, l6, p11, l4 – 20, p13, 3 - 4).*

Sincerely yours,

Mitsugu Hachisu　Ph.D., Professor

Showa University