Author's response to reviews

Title: A Pilot Randomized Controlled Trial to Improve Geriatric Frailty

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

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We are most happy to resubmit the above mentioned manuscript after careful revision for consideration of publication in BMC geriatrics. We appreciate the constructive opinions of the reviewers that pointed out many concerns for the manuscript. We have answered the critiques and questions point by point in the following “responses to reviewers. The manuscript is revised accordingly.

Frailty is an increasingly recognized geriatric syndrome characterized with loss of reserves (energy, physical ability, cognition, health) that gives rise to vulnerability. However, there was generally lack of agreements on measures of frailty and optimal management strategy is still evolving. Our study addressed to those questions that we thought important. We hoped our study will provide some information to the readers of the journal.

The manuscript is an original research that has not been published and is not under consideration elsewhere.

We hope our revision is up to your expectation and standard. We are looking forward to your favorable response.

Sincerely yours,

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Response to Reviewer Comments:

Reviewer 1: Marta Castro

Major compulsory revisions:

It is necessary to define: frailty instruments, operationalizations of frailty, frailty status, because it leads to confusion

Why the authors change 5 kg by 3 kg for smaller body size for East Asian population and why do they not change walking speed and grip strength if these issues are influenced by body size too?

Response: Thanks for your comments. We created a new table 1 in revised manuscript for the detail of the operationalization of the Fried’s instrument.

At the time of designing the study, there was no epidemiological study in Taiwan to provide evidence based cut-point of each variable. Therefore, most of the cut-points used in the Cardiovascular Health Study were adapted. The reason for use 3kg instead of 5kg is based on the fact that most Taiwanese older adults weigh in 60-70kg ranges. If we used 5% of the body weight change as the cut-point, the number is roughly 3kg.

Therefore accordingly, we modified the recruitment and eligibility section, third paragraph on page 8 into:

The CHS_PCF was used to select eligible participants. Most cut-points were adapted from the CHS (Please refer to Table 1 for detail). Important modifications were: Weight loss of 3kg (instead of 5kg) was used to adjust for smaller body size for an East Asian population. The Taiwan IPAQ-SF (International Physical Activity Questionnaire Short Form) instead of the Minnesota Leisure Time Physical Activity Questionnaire was used to measure energy expenditure because the former has been validated in Taiwanese populations.

We also insert an additional limitation in “Strengths and Limitations of the Current Study” part of the discussion section as follow:

Forth, we did not have use population specific cut-points in the 5 frailty indicators to enroll study participants. At the time of the study design, Taiwanese frailty cut-points with the CHS_PCF were not available. However, since it is an interventional study with a purpose to identify subjects with certain degree of frailty suitable for interventions, it probably did not matter which cut-points were used as long as study populations could be clearly and systemically identified and classified.
To clarify what do you mean with "instruments could generally fit into 3 dimensions (What dimensions???) with 8 factors (what factors???)

Response: Thanks for your comments.
The three domains are physical, psychological, and social domains. The eight factors include nutritional status, physical activity, mobility, energy, strength, cognition, mood, and social relationship/social support

For clarification, we revised the third sentence, first paragraph on page 5 of background section to:
A recent review of frailty instruments as outcome measures found that instruments could generally fit into 3 dimensions (physical, psychological, and social) with 8 factors (nutritional status, physical activity, mobility, energy, strength, cognition, mood, and social relationship/social support).

To separate disability of frailty: why are the authors excluding scores of 1, 2 or 7 by CCSHA_CFS_TV, because they are too much frail or too little frail? Or because they are too disabled?

Response: Thanks for your comments.
In this study, we intended to enroll subjects with some degree of frailty or pre-frailty for intervention. Subjects who scored 1 (very fit) and 2 (well) without active diseases by the instruments are considered too healthy for the study. On the other hand, subjects who scored 7 (severely frail) were completely dependent on others for ADL would not be able to participate in the study exercise program. Therefore, they were excluded as well.

We have revised the last sentence of recruitment and eligibility section, first paragraph of page 6 to:
Exclusion criteria included institutionalizations; communication barriers; and scores of 1, 2, (too healthy) or 7 (too ill) on the CCSHA_CFS_TV.
Reviewer 2: Armold Mitnitski

Major Compulsory Revisions

1. I would like to see more details of using GEE model mentioned in the method section. If you used such an approach it should be spelt out - it is not sufficient to say that GEE was used - it is a generic techniques and may mean different things. The other question is does it necessary to use GEE in your study?

Response: Thanks for your comments. In our study, the generalized estimating equations (GEE) model was used to compare the between-group frailty improvement with adjustment for time and treatment-by-time interactions. We used GEE in our study because the outcomes of interest (e.g., frailty improvement) were measured at several time points (baseline, the 3rd month, the 6th month, and the 12th month). In this situation, generalized Linear Model may not be an optimal choice. The GEE or repeated measure ANOVA are more appropriate methods instead. Comparing GEE with the repeated measure ANOVA, GEE have more advantages. For example, GEE allows for covariance structure other than compound symmetry (exchangeable), which was the assumption of repeated measure ANOVA. For repeated measures without missing observations, GEE yields the exact same results as the repeated measure ANOVA. When there is a missing value for an individual, GEE can still use the individual’s information. The repeated measure ANOVA, however, will delete the whole information for the individual (list-wise delete) and only use the rest complete data. Thus, we think it is appropriate to use GEE in our study.

We revised the approach to analysis section, third paragraph on page 12 to 13 as following:

In our study, the outcomes of interest (e.g., frailty improvement) were measured at several time points (baseline, the 3rd month, the 6th month, and the 12th month). For estimating the repeated measurements of the intervention effect, the generalized estimating equations (GEE) model was used to compare the between-group frailty improvement with adjustment for time and treatment-by-time interactions. GEE approach is an extension of general linear model (GLM) and provides a semi-parametric approach to repeated categorical response. The intervention effect can be reasonably estimated by using GEE even if the covariance structure is not specified correctly.

2. In the introduction, you mentioned that you used CCSHA for the first stage screening. Still, you had chosen the CHS to classify frailty. My question is: would it
be possible to use the CCSHA as an outcome?

Response: Thanks for your comment. The CCSHA telephone version was used only at the screening stage, not repeated during the follow up period, we were not able to use this instrument as an outcome.

3. One limitation of the study is rooted in the application of the Fried criteria which does not allow assessment of the different degrees of frailty. The other approaches (e.g. CCSHA) could found improvements of health in people with different degrees of frailty (not only frail/pre frail). I encourage you to discuss such a possibility.

Response: Thanks for your comments. Because we did not measure CCSHA repeatedly, we would be unable to explore the possibility. In the Strengths and Limitations of the Current Study part of the discussion section, page 21 second paragraph, we added:

Third, the CHS_PCF instrument does not allow assessment of different degrees of frailty as the CCSHA_CFS_TV. However, we were not able to detect more subtle changes frailty degrees with the later instrument since it was only used at the screening stage.

4. Some additional references would be useful to consider. It was known from observational studies that frailty is a dynamic process and its improvement is possible. Here are three relevant references:


Response: Thanks for your comments and providing references. We have included those references (references 33,34 and 35) into our manuscripts.

Following the method, of the Gill TM et al 2006 paper, we created a new table (table 3) to be included in the result section.

In response and discussion of these three references, in the discussion section, second paragraph, page 20 we added this new paragraph to discuss the
transition of frailty status.

Some observational studies suggested that frailty is a dynamic process and natural transitions to better status may occur without interventions. During the intervention period, our degrees of improvement in frailty status were significantly higher than the natural improvement rates reported from observational studies. On the other hand, the improvement rates during the follow up periods were similar to other studies.

5. Because there are only 3 groups of Fried frailty it would be worthwhile to see the table with the numbers of transitions between all frailty states. My bet is the most improvements were from pre-frail to robust states. It would be interesting to see how these changes by the different intervention groups.

Response: Thank you, we do agree with you. In order to make this point, on the results section, we added a new paragraph (page 15, second paragraph) to explain the transition of frailty status (Table 3).

During the intervention period (baseline to 3-month), 33 (32.4%) of the pre-frail participants (N=102) improved to robust, while 3 (20%) and 6 (40%) of the frail (N=15) participants improved to robust and pre-frail, respectively (Table 3).

During follow-up periods without intensive interventions, most individual stayed at their original status, the chances for natural transition to better frailty status was a lot fewer. For example, during the 3-6 month follow up period, only 2 (22.2%) of frail individuals (N=9) improved to pre-frail status, and only 12 (16.7%) of pre-frail individuals (N=72) improved to robust status.

6. There is no reference to the results mentioned in the supplementary materials expect mentioning Additional files provided with this submission at the end of the manuscript. The reader has to guess what is there- much more details should be given if the authors think that the tables are of any importance. I personally do not see any reason to use the supplementary tables in the BMC Geriatrics. It is an electronic journal that imposes no limitation on the number of figures and tables. These tables could be arranged in Appendix if you think it would disrupt the presentation flow.

Response: Thanks for your comments. We changed the supplement tables to appendix tables and uploaded the tables for review.

In the results section, page 17, two tables were referred to as Appendix Table 1 and Appendix Table 2.