Author’s response to reviews

Title: Fish protein supplementation in older nursing home residents: a randomised, double-blind, pilot study

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Reviewer #1: Report on Paper PAFS-D-18-00215

The authors report on the results of a pilot RCT of a fish protein supplementary diet in nursing home patients. They postulate that fish protein supplementation may beneficially influence age-related muscle loss. The protein supplement was successfully administered to those taking part in the study but recruitment was a major issue. Biological results are presented.

The paper is presented in a form suitable for publication and the English is of a satisfactory standard requiring only a minimum of sub-editing e.g. line 28 "is" changed to "are". The paper is on the lengthy side and I wonder whether all the content is necessary e.g. details of how the fish protein is processed.

We thank the Reviewer for these comments. We have corrected the spelling error in line 28 and we have thoroughly checked the manuscript for additional spelling errors. We agree with the Reviewer that some details regarding the processing of the fish protein can be removed from the text, and in the revised form of the manuscript the length of this section has been reduced (lines 157-166). In addition, the discussion section has been revised with the aim of reducing the length of the manuscript.
Specific comments

Abstract
Line 36: Mention how participants were screened for nutritional risk and ADL.

Information on how participants were screened for nutritional risk (Mini Nutritional Assessment) and ADL (Barthel Index) has been added in the abstract section, lines 36-37.

Line 43: There are other benefits for using multiple sites other than just recruitment.

We agree with the Reviewer that using multiple sites will result in benefits beyond improved recruitment such as a more heterogenous and possibly a more representative study population and a reduction in the influence of systematic errors on the results. Due to the word limitation in the abstract section a statement regarding other benefits of using multiple sites have been included in the discussion section (lines 378-380).

Introduction

The biological rational for the study is presented and experimental results in rats have been summarized.

Methods

Line 96. The study is described as randomized but then allocation was stratified by the project manager. Please explain.

We apologize for not describing the randomization process properly. All participants were stratified according to sex, age and weight before randomization to one of the two experimental groups. In the revised version of the manuscript the description of the randomization process has been corrected (lines 102-103).

Line 98. How many were recruited using the sarcopenia criteria and how many following the change in admission criteria?
The admission criteria were changed during the first week of recruitment and all participants included in the study followed the changed admission criteria. This information has been included in the methods section (lines 108-111).

Line 108. Were these the original criteria? This statement is not compatible with "all elderly nursing home residents (line 102).

We apologize for not describing the change in inclusion criteria clearly. We have revised the method section describing study design (lines 108-111).

Line 132. Did fish protein influence the taste of the drink? Were subjects asked whether they believed they had the fish protein or the placebo? Although the subjects may have been blind to the intervention, the staff was not. Did you consider a placebo powder? Did the fish powder all come from the same batch?

The Reviewer raises important questions about the administration of the fish protein supplementation, as the smell and taste of the fish protein are challenges for design of studies of this kind. Before study-start we tested various ways of distribution and masking of the fish taste and odour (such as chocolate powder and different soft drink flavours) and found that the taste and smell of the fish protein powder were efficiently masked by the flavour of the lemon/lime and strawberry/kiwi soft drinks. All participants were regularly asked how the drink tasted and if they experienced any distaste when consuming the drink. A distaste of the drink was reported only once by one participant, and we believe this incident was due to a mixing error by the nursing home staff.

We did not ask the participants if they believed they received fish protein of placebo, and this could be done in a full-scale study to check that participants were properly blinded.

In the current study, the staff working at the nursing homes could not be blinded since they prepared the drinks for the participants. Since the fish protein powder holds a specific smell using a placebo powder would not result in blinding of the staff. We therefore chose to use a soft drink without added protein in the placebo group in this pilot study. As stated in the discussion section (line 390), ready to serve drinks should be used to reduce the work load for the staff and to ensure blinding of the staff in a full-scale study. A statement regarding blinding has been added in line 391.
The fish protein powder used in both study periods came from the same batch.

Line 146. Explain purse seiner please. Is this a standard method of fish protein manufacture used for other purposes?

A purse seiner is a fishing vessel used for fishing pelagic species. In the revised version of the manuscript this term has been omitted. The method for fish protein production has been revised with the aim of reducing the length of this paragraph (lines 157-166). The method for fish protein hydrolysate production is not standardized and we believe that some details regarding the production are necessary to allow others to reproduce the present study.

Line 188. What is meant by medically sound?

By medically sound we meant medically safe; i.e., that it was regarded as safe to postpone the administration of medicines for the participants to after the blood sampling. The term “sound” has been changed to “safe”, line 210.

Line 196. Mention MNA and Barthel in abstract.

MNA and Barthel ADL index has been specified in the abstract section (lines 36-37).

Line 228. Is this paragraph necessary? Was there a primary outcome.

We agree that this paragraph is not necessary as this information is described in the introduction, in the last paragraph describing the aim of the study (lines 90-93). The primary outcome was to assess the feasibility of the study.

Line 234. I would conclude this sentence after two experimental groups.

We agree with the Reviewer and in the revised version of the manuscript we have concluded the sentence after “two experimental groups”.

Results

Line 255. How was intake measured?
Intake was measured as a 24-h dietary registration conducted by the nursing home staff, this is described in the methods section (lines 226-227).

Line 255. Primary outcome should be presented first and then secondary outcomes.

We are not sure if we understand the Reviewer’s comment. The primary outcome of the present study is the feasibility of the study. Participant characteristic, including participant flow and drop-out was considered important aspect of the primary outcome. In the revised version of the manuscript we have also included information about the number of nursing homes contacted and the number of nursing homes who entered the study (lines 271-272) and included a statement about the feasibility of study conduction (lines 274-275).

Discussion

This should be reviewed with the aim of reducing the length. Much of the paragraph at line 302 is a repeat of what has been stated earlier.

The discussion section has been reviewed and the length has been reduced. We have deleted much of the paragraph from line 321 and removed the discussion about the potential benefits of fish proteins.

Is the discussion about the potential benefits of fish protein relevant here?

The discussion has been revised with the aim of reducing the length. We agree with the Reviewer that discussing potential benefits of fish protein is less relevant and these sections have been deleted in the revised version of the manuscript.

I liked the section at line 344.

Do you not also need to consider how benefit in cognitively impaired people may be assessed? By excluding such patients you may limit generalization of results.

We agree with the Reviewer that excluding cognitively impaired people may limit the generalizability of the results. We chose to not include nursing home residents with impaired cognitive function in this pilot study to ensure that our participants could give us feedback on how they experienced the study design, as we considered this information important when
assessing the feasibility of the study and planning the full-scale study. Future studies should consider the inclusion of older adults with cognitive impairment to ensure a study population that is more representative for the nursing home population. A statement regarding the inclusion of older adults with cognitive impairment has been included in the discussion section (lines 381-382).

Table 2. As there were no differences between groups why not just say so in text and omit this table?

Table 2 holds information about participant characteristics such as mean age, anthropometric measurements, number of medical diagnoses and medications and nutrient intake and we have considered this information valuable despite the lack of differences between the groups. We have therefore chosen to keep Table 2 in the manuscript.

There should be a full Consort chart starting with number of nursing home residents as this is how you eventually conducted the study (according to text).

The flow chart has been updated to include number for nursing homes contacted and number of nursing homes interested in participating in the study. Unfortunately, we do not have the total number of nursing home resident in the different nursing homes, therefore this information is not included in the chart.

Reviewer #2: This is an interesting paper. As I pilot study it has high lighted issues regarding recruitment. There are no definite endpoints but this is expected in this type of study. The pilot should have outcomes that would be related to a more definitive study. I.e. what level of recruitment and retention needs to be reached for a full study to go ahead.

Why was the protein provided as a powder and not a tablet. This would have got over any particular taste issues.

Based on previous experience using tablets with fish protein hydrolysates, a supplementation of around 5 grams/day would require the participants to consume more than 40 tablets per day. Also, the characteristic fish protein smell will be evident in tablets. In collaboration with the nursing home department it was decided that a powder protein supplement given as a drink would be most suitable for this population group.
There are a few points to highlight

1. The introduction should contain a comment regarding the inefficiency of converting protein ingested to muscle protein.

We have included a statement about anabolic resistance observed in the older adult population in the introduction (lines 65-70).

2. The term elderly should be changed to older people

The term elderly has been changed to older people.

3. The definition of older people needs to be stated as 60 is not old.

We agree that the definition of older adults in the manuscript is unclear. We thank the Reviewer for making us aware of the inconsistency in our inclusion criteria which includes adults aged 60 years or older, while the more common definition of older adults is 65 years or older. In the present study the mean ages of the two groups were 84 and 87 years, and the youngest participant in our study population was 68 years old. Thus, all participants can be defined as older adults. The age range of the participants has been included in the results section (lines 277-278) to clarify that all participants met the common definition of an older adult. We agree that the inclusion criteria should have been set to age 65 years or older and this will be corrected in a full-scale study.

4. Why nursing home residents and not frail older people in the community. It may be better to recruit those that are pre-frail or CFS 5 rather than 6-7 as it may be too late.

We agree with the Reviewer that it would be of interest to investigate the fish protein supplement in pre-frail community dwelling older people. This population may be easier to recruit and the potential for preventing age-related loss of muscle mass and strength may be higher. In the present pilot study we wanted to investigate the feasibility of conducting an intervention study in the nursing home setting and therefore chose this population rather than the community dwelling frail older adults.

Further, the inclusion of community dwelling elderly would lead to some logistical challenges. Most important; as the protein supplementation had to be prepared daily the participants would have to mix the protein powder in the drink themselves, making blinding impossible. In addition,
we anticipated that it would be challenging for many of the pre-frail older adults to attend regular study visits and we did not have the resources to conduct home visits to the community dwelling participants.

5. Functional outcomes should be included such as the Timed Up and Go. An increase in muscle strength without an increase in function may demonstrate limited benefit.

We agree with the Reviewer that functional outcomes such as the Timed Up and Go test should be included in addition to measurements of muscle strength. Unfortunately we did not have the personnel to conduct testing of such functional outcomes in this pilot study, however this will be a priority in a full-scale study.