Author’s response to reviews

Title: What are the most effective interventions to improve physical performance in pre-frail and frail adults? A systematic review of randomised control trials.

Authors:

Tara Kidd (t.m.kidd@ljmu.ac.uk)
Freda Mold (Freda.mold@surrey.ac.uk)
Claire Jones (Claire.jones@surrey.ac.uk)
Emma Ream (e.ream@surrey.ac.uk)
Wendy Grosvenor (w.grosvenor@surrey.ac.uk)
Martha Sund-Levander (Martha.sund-levander@liu.se)
Pia Tingstrom (pia.tingstrom@liu.se)
Nicola Carey (n.carey@surrey.ac.uk)

Version: 1 Date: 30 May 2019

Author’s response to reviews:

Tovah Aronin
Editor-in-Chief: BMC Geriatrics

30/05/2019

Dear Dr Aronin

Ref: BGTC-D-18-00297

We should like to resubmit our paper entitled Effectiveness of nutritional and physical activity interventions on physical performance in pre-frail and frail adults: a systematic review of randomised control trials to BMC Geriatrics. We would like to thank the reviewers for their helpful comments. Please see our responses to the comments below.
Response to comments

Please note all changes are highlighted in the text.

Reviewer 1

1. This article deals with an important societal issue. While the study has been performed rather well, it seems a little bit strange in the beginning that physical activity and nutrition have been combined. In addition, there is sometimes lack of coherence e.g. in the title the two aspects have been described, while in the discussion (in the abstract) there is only a reference to physical activity.

The co-occurrence of physical activity and nutrition is not uncommon in the research literature or within clinical settings, particularly for older populations. Many studies are now using multi-domain interventions to prevent/improve physical frailty symptoms (e.g. Dedeyne et al., 2017). The rationale for this is clear given the physical phenotype characteristics of frailty (BMI, loss of muscle strength, exhaustion, slow walking speed, reduced activity). This is reflected in the studies that have included in the review. The focus solely on physical activity in the discussion section of the abstract is because we feel this best represents the main finding of the review within the constraints of the word allowance; specifically that physical activity was found to be the most efficacious intervention to improve physical activity in this population.

2. The rationale to focus on nutrition and physical activiy however becomes clear in the introduction where it is clearly stated that the criteria of Fried have been used to operationalize frailty. I do agree with that, however, this is a very narrow way of looking at frailty, but from this perspective the combination of Physical activity and nutrition is logical. I would suggest to add some additional information regarding the bio-psycho-social phenotype (e.g. Gobbens) and put this in a broader picture. Certainly because the authors argument that there is a lack of clear criteria for frailty. It might be interessting to add in the title that it is about physical frailty. Certainly becasue in the included articles different definitions and operationalidations of frailty were used.

The reviewer raises an interesting point regarding the biopsychosocial phenotype; however, we feel that it might set up false expectations to present this in the introduction section, that we are then not able to deliver on as we did not did not examine this in the review. We also understand the reviewer’s point about inclusion of physical frailty in the title. This was discussed during the paper preparation but as some of the participants were either not frail or prefrail we felt this would not be appropriate and feel the term physical performance provides a more accurate representation of the outcomes examined in this review. Based on the reviewers comments in this and previous points, we have changed the title to reflect the broader remit of the review.
3. By the way; nutrition is not in the key-words, while physical activity is. I would suggest to add this to the key-words.

#Apologies, this was an oversight. This has now been corrected.

4. The method has been described welll. Some remarks, how did the authors managed it to go from 2511 results to 33. The flowchart is clear, but how exactly did the authors screened 1709 records? That is a lot of work, and it seems that the search terms were not specific enough. This also shows the lack of coherence between the introduction and the method. From the introduction one could conclude that the search terms would have been 'nutrition' and 'physical activity', but this is not the case. The key-words have been kept very broad. While reading the article I did get confused and it seems as if the introduction has been written after the results were clear. Not vice versa. The research question is not about nutrition and physical activity, while the introduction leads to the expectation that it is.

#We agree with reviewer 1 that the search terms were broad. We have now included this in the limitations section of the discussion. The search terms arose from a piece of commissioned work that wanted to examine early interventions and physical frailty. The studies that fit the criteria of early intervention and frailty were physical activity and nutrition interventions. This was established by a small team of researchers (n=6) who initially scanned the articles, which were then checked independently by 2 other reviewers. We respectfully disagree with the reviewer that we build up an expectation that the search terms will be physical activity and nutrition. We discuss physical activity and nutrition in the introduction due to the predominance of these types of intervention in this population. The focus of the introduction is describing the phenotype, the current issues around frailty, and the problems associated with measuring improvements in frailty symptoms vs. physical performance outcomes, which corresponds to our research question, and search strategy. What our review highlights is that there are limited approaches to the treatment of physical frailty.

4. About study selection and screening. no kappa statistics have been used? the authors have used discussions in teammeetings. This seems very hard to get to a conclusion. See also remark about the amount of articles. How was the pre-defined extraction form was developed?
The data extraction form (DEF) contents/layout was based on previously used form used in other published reviews, but was adapted to include information retrieval pertinent to this specific review.

There is considerable controversy surrounding the use of Kappa statistics for inter-rater reliability due to the difficulty in interpreting indices of agreement. This has led researchers to use discussion as a simpler approach to evaluate any disagreement between items.

5. It is unclear how the authors have included the studies and were sure that the studies were about frailty. In table 1 some frailty criteria were given, but not a real frailty measure. That questions whether all included studies were about frailty, or just about older persons having one or more physical problems.

Currently there is no standardised measure of frailty, and therefore we included studies that had a measure of frailty that incorporated one or more of the physical frailty criteria outlined by Fried et al. 2001. In our inclusion/exclusion criteria we are clear that if there were no physical frailty indices the studies were excluded. We wanted to include pre-frail individuals as well as frail, as we wanted to examine prevention (early intervention), as well as delaying progression of physical frailty symptoms. As per Fried et al., 2001 pre-frail individuals may only fit one or two of the criteria. Unfortunately few studies reported the numbers of those who were classed as frail, pre-fail, or non-frail. We agree with the reviewer that this is an important limitation which we do address in the discussion.

Reviewer 2

1. This is a well-written review that examined the effectiveness of nutritional and physical exercise interventions in a frail population. The review is registered in Prospero and reported following the prisma guidelines. It would be really good if the authors could apply following issues:

- Estimating the effect size of the outcomes found in the different analysed studies would, together with the risk of bias analysis, improve the outcome analysis.

# We believe that given the heterogeneity of the measures used to assess frailty and the subsequent mix of frailty status within studies, the different types of intervention, and the variation in outcome measures used, effect size calculations are somewhat redundant and potentially lead to a distortion of the results. If frailty status was relatively equal across studies then calculating effect size and/or meta-analysis would be fruitful as we could compare across the studies. This is why we felt a literature review was the most appropriate way to present the findings.
2. Physical activity is not the same as physical exercises. You use the term physical activity, but I think you mean physical exercises. Since physical activity is 'unstructured activities incorporated in daily life', you should switch the term you use to physical exercises.

# We deliberately used the term physical activity as it includes a wide range of movement that can improve physical performance. Physical activity is the term most often used in relation to older and or frail populations where “exercise” might not be possible or preferable. Some of the studies included in the review reflect this, as they look at activity in relation to being able to get out of bed, or walk unaided using physical activity mobility plans for example. We feel that physical activity is more inclusive and representative of the populations studied in the review.

3. Typing mistakes in abstract (line 24 ; after activity, line 29 component(s)); Keywords: why not include nutrition?

# Nutrition has been added to the keywords.

4. Introduction: P 3 Line 10: 4-60% adults are frail. Please explain this wide range; P 4 line 10: body mass and … (physical) activity levels

# We report the statistics on estimated levels of frailty prevalence taken from the research literature. We do explain throughout the paper that one of the major limitations with frailty research is a lack of standardisation in terms of definition and agreed criteria. This lack of agreement translates into a wide ranging estimate of prevalence.

P 4 line 10: body mass and … (physical) activity levels

# Would it be possible for the reviewer to elaborate on what they mean here?

5. Methods: Why is the search limited in time? March 2017 is 2 years ago, is a new search from then till now possible? Why not include studies before 2010? Please give a reason or perform a new search.

# Studies before 2010 were excluded as several reviews had been done that included this time period (e.g. Landi et al., 2010). We originally submitted this paper over a year ago to BMC geriatrics, at the time we had updated the search; however, due to financial constraints we are no longer able to provide further resources to keep updating the review during this process.
6. Search strategy: very good to look for articles in a wide range of databases, although why frail had to be combined with both early intervention and health care is not clear.

# We were interested in interventions to prevent frailty as well as delay symptom progression which is why the term early intervention was included. In addition we were interested in examining interventions across primary and secondary health care settings, which is why health care was also included. We do discuss the need to identify effective interventions that promote successful aging and minimise burden of care on health care services in the introduction. We also discuss the implementation and success of different interventions across primary and secondary health care in the results and discussion.

7. A lot of articles were found by other sources, maybe implying that the strict use of AND resulted in a lot of missed articles. I think of one article I am missing in this review: Tieland, M., et al. (2012). "Protein supplementation increases muscle mass gain during prolonged resistance-type exercise training in frail elderly people: a randomized, double-blind, placebo-controlled trial." J Am Med Dir Assoc 13(8): 713-719. This article was probably excluded. Can you please elaborate on the reason?

# This was excluded on the basis of similarity with this paper which was included in the review:


8. Population targeted is frail population, however, several studies used a mixed population with also non frail participants. This leads to distortion of the results.

# We agree and highlight this in the limitations section. We also stress that the results must be interpreted with caution for this reason. Unfortunately it is quite common in this area of research. Correspondingly, this is one of the reasons why we believe calculating effect sizes is not useful.

9. In additional file 1: please change in the legend the Ab to AB and Ti to TI for consistency

# This has been corrected.

- Please rephrase eligibility criterion 2, P 6 line 52: why use an abbreviation (DEF) when you no longer use them further in the text).

# The changes have been made.
10. Physical performance is defined as a measure of body mass index, which is odd. The rationale to include BMI was not given.

# BMI was included as weight loss is one of the 5 frailty criteria (Fried et al., 2001) which we outline in the introduction. BMI is the gold standard method to assess weight gain or loss in the research literature with many journals refusing to accept studies that report simply the percent of weight lost as the sole descriptive index (e.g. Deitel & Greenstein, 2003). BMI is an indicator of a physical change, similar to walking distance, or hand grip and fulfilled our outcome measure requirements. This has been clarified in the definition of terms in the method section.

11. Bias assessment: when the classification of the bias was unclear, were the authors contacted? This is perfectly possible since all the studies are recent.

# No, this was not possible. We were a small team, and had no resources to follow this through. This process is in line with the procedure to conduct a Cochrane review (Chandler et al., 2017).

12. Results: Figure 1: flow diagram: 38 records were found through other sources, however, the origin is not explained. Please elaborate on this.

# Other studies were identified by looking through the reference lists of included studies.

13. P 7 line 31: explain how you did the additional searches

# Please see comment above.

14. P 7 line 58: I do not see how appendix 2 (with studies reported with low or unclear quality) lead you to the last sentence 'methodological quality (n = 3) ranged from adequate to excellent (n = 7)'. I do not understand how you included the studies labelled as 'unclear' are given an adequate or excellent quality.

# We examined both risk of bias and methodological quality in the review. The bias findings are presented in the appendix. According to the Cochrane handbook, “Bias may be distinguished from quality. The phrase ‘assessment of methodological quality’ has been used extensively in the context of systematic review methods to refer to the critical appraisal of included studies. The term suggests an investigation of the extent to which study authors conducted their research to the highest possible standards. This Handbook draws a distinction between assessment of methodological quality and assessment of risk of bias, and recommends a focus on the latter.” This is because a study may be performed to the highest possible standards yet still have an important risk of bias. We acknowledge in the review that the studies have a range of methodological quality but we are unable to ascertain the risk of bias.
15. P8 line 44: 'the' Netherlands; line 46: Remove the sentence 'No studies originated from the UK'; line 51: P9: please revise the use of the term 'physical activity'

# Respectfully, we feel it is important to highlight the lack of studies in the UK, especially as we are UK based researchers. The lack of RCT trials in the UK is an important issue that needs to be addressed, especially given the fact that the UK Government strategy to improve health outcomes by 2020 includes targeting frailty and ensuring independent living for older adults (PHE, 2019). We have clarified this further in the conclusion.

16. The results section is difficult to understand because the text is almost a textual rendering all the minute details normally provided in table format, of all the studies. The text is structured according to the care setting they were provided in, however, this does not contribute to the understanding of the text since the importance or results based on setting are not explained. To be more than a useful extraction of data, the author must also analyze the data in such a way that he/she highlight the overarching findings, and delete all the minute details. These details are already well covered in the tables provided, and need not be repeated in the text.

# We have considered the reviewers comments along with those of reviewer 1 in relation to the results section. While reviewer 2 felt the results were too detailed, reviewer 1 did not have any issue with the level of detail provided and deemed it entirely appropriate for a literature review article. We believe that the minute details are necessary given the heterogeneity of the studies to enable us to find a commonality between the studies. Correspondingly, the text was deliberately set out across primary and secondary settings to try and elucidate what works well, for who, and where is it best to deliver the intervention. Understanding this is crucial if we are to deliver on the UK Government strategy of better outcomes by 2020, using key strategies such as prevention, early identification, and treatment. Currently there is no evidence base to support where this provision would be most efficaciously delivered. Given the lack of funds for healthcare provision (nationally and internationally) there is an urgent need for evidence based interventions that deliver optimal results.

We hope that we have answered all of the points of the reviewer and made the appropriate changes in the manuscript to their satisfaction.

Yours faithfully,

Dr Tara Kidd (C.Psychol).