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Title	The effectiveness of nutrition and combined nutrition plus physical activity interventions in older adults living with frailty or pre-frailty: a systematic review and meta-analysis
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Reviewer 1	Thomas Brothers
Institution	Department of Medicine, Faculty of Medicine, Dalhousie University, Halifax, NS
General comments (author response in bold)	<p>"Potentially relevant, related literature that does not recognize frailty explicitly. The authors define in their eligibility criteria that the trials must identify study participants using a valid frailty measurement tool, as the aim of the systematic review is to inform forthcoming clinical practice guidelines for frailty. However this raises a common and important issue in frailty research (and in the development of clinical practice guidelines for frailty) where potentially informative studies using other geriatric syndromes or other signifiers of an age-related vulnerability state (besides frailty; eg., sarcopenia or falls) are not included. In the case of nutritional interventions, there are multiple randomized studies that might be informative including participants identified as sarcopenic, or as part of an intervention after a fall. E.g.:</p> <p>Rondanelli M, et al. Whey protein, amino acids, and vitamin D supplementation with physical activity increases fat-free mass and strength, functionality, and quality of life and decreases inflammation in sarcopenic elderly. <i>Am J Clin Nutr</i>. 2016;103(3):830-840. doi:10.3945/ajcn.115.113357</p> <p>Englund DA, et al. Nutritional Supplementation With Physical Activity Improves Muscle Composition in Mobility-Limited Older Adults, The VIVE2 Study: A Randomized, Double-Blind, Placebo-Controlled Trial <i>J Gerontol A Biol Sci Med Sci</i>. 2017;73(1):95-101. doi:10.1093/gerona/glx141</p> <p>Based on the specific aims and design of the study, trials such as these were not included, as they do not specifically identify participants as frail using a valid frailty measurement tool. While they do not specifically use the language of frailty, they do identify frail adults (as sarcopenic older adults with comorbidities are frail, and older adults with mobility limitations and comorbidities are frail). Some studies in other settings use slow walking speed or weak grip strength or low muscle mass alone as markers of "frailty", and define "frailty" as such in their papers. For example Kim, 2013 (Reference #26 in the present manuscript), defines "frail" as slow usual gait speed or poor nutrition. Would Rondanelli et al have been included if they included a sentence stating that sarcopenia is a marker of frailty, or Englund et al if they said mobility limitation/slow gait speed was a marker of frailty? A narrow, specific focus on the semantic label of frailty (even before the scientific community has decided on a single best operational definition of frailty) may exclude important information which would otherwise be clinically relevant."</p> <p>"We appreciate the recognition of literature that may not have been included in our review. There are studies that potentially included frail patients that we did not include. However, they did not measure frailty in a systematic manner and from a generalization point of view this is very problematic. Using studies that measured frailty using a validated tool allows the results to be generalized. The authors feel the strength in this review is the clarity of</p>

the population, and in doing so, this highlights the need to use clear definitions in future research. This review seeks to be different and encourage future studies to use a formal or working assessment of frailty is performed. It is also important to note that inclusion wasn't only based on use of a frailty tool, given the fact that the definition of frailty has changed in the last decade. Other author-specific criteria were also established so that it was evident and clear exactly what constituted pre-frail/frail participants in the studies.

Our review was up-front and selective in defining our population. We feel that future studies need to do better job of defining this group, and reducing the overlap with other geriatric conditions, so we can see effectiveness of interventions. Our review sought to address this gap in the literature.

To address these reviewer's concerns, we have added to the introduction a brief description about our novel take on the literature and a citation about the importance of screening

(DOI: <https://doi.org/10.1017/S0714980816000301>). We have also added to the discussion/limitations that we may not have covered all literature because of our strict definitions. "

Frailty measurement scales.

Results, lines 185-186: "The 2 most common tools used to measure frailty status in the participants were Fried's Frailty phenotype (36) and the Cardiovascular Health Study Criteria (36)." In my reading of Reference #36 (Fried et al), Fried's Frailty Phenotype and the Cardiovascular Health Study Criteria are the same measure. The authors could consider describing this as the single most common tool, or otherwise describe how they differ.

Revisions have been made and all studies have been reviewed for modifications of frailty tools. These measures can be combined. They are similar, but were described as such in papers (some said Fried vs others said CHS) and were thus captured this way for transparent reporting in the manuscript. Fried's criteria were derived from the Cardiovascular health study and such can be considered the same. Fried's has 5 criteria and it is how they are measured that are modified rather than the criteria themselves as in the study cited by the reviewer.

I believe it is also important to highlight modifications to the Fried Frailty Phenotype/CHS criteria or other pre-determined frailty criteria where they occur, as modifications may have important implications for participant inclusion, variance in outcomes, and assessments of prevalence/incidence (see e.g. Theou et al., Modifications to the Frailty Phenotype Criteria. Ageing Res Rev. 2015 May;21:78-94. doi: 10.1016/j.arr.2015.04.001). This is described in some parts of the paper (e.g. it is noted that the Fried Phenotype criteria are modified, or rather that the authors indicated it was modified, in Niccoli, 2017 and Wu, 2018). However, the Frailty Phenotype/CHS criteria are also modified from the original criteria in Ng, 2015 (all 5 criteria are modified) and Kim, 2013 (only 2/5 criteria are used and these are both modified). There may be modifications in other studies that did not report them as well.

Specific and detailed modifications of frailty tools were already described in appendix 3 (characteristics of included studies table) as they were reported in the studies. Additional details have been added where available and updated in corresponding tables and text.

	<p>"Minor issues (wording, formatting, etc.): Figure 9: It appears the top forest plot is for continuous frailty outcome measures and the bottom forest plot is for binary frailty outcome measures. While "continuous and binary" are mentioned in the Figure legend, the authors could consider making this clearer for the reader eg. Changing it to Figure 9a and Figure 9b. The authors could consider providing further details in all figure legends to help interpret the figures when they are read on their own." We have edited and revised all of the figures to meet the requirement of 4 total. We have taken into account these suggestions to help with clarity of the new figures.</p>
Reviewer 2	Larry Chambers Dr. Chambers
Institution	Elisabeth Bruyere Research Institute, Ottawa, Ont.
General comments (author response in bold)	No substantial comments to address
Reviewer 3	David Hogan Dr. Hogan dhogan@ucalgary.ca
Institution	Department of Medicine, Health Sciences Centre, University of Calgary, Calgary, Ont.
General comments (author response in bold)	<p>Conflicts of Interest: The authors have no link to any commercial entities, but a number of them are employed by/ have links with the funders of the study (e.g., Dr. Muscedere is the Scientific Director and CEO of the CFN, Dr. Holroyd-Leduc is chair of the CFN knowledge translation committee and member of the research management committee, and three other authors I believe work for CFN). These relationships would raise the possibility of intellectual conflicts of interest. I don't see this as a major issue but feel they should be noted. We have provided a more robust response of the transparent process conducted to synthesize results. None of the authors had an interest in the decisions made. CFN has copies of COI forms for all steering committee and project members.</p> <p>Introduction: Not all relevant systematic reviews on the topic at hand were noted (e.g., Kidd T, Mold F, Jones C, et al. What are the most effective interventions to improve physical performance in pre-frail and frail adults? A systematic review of randomised control trials. BMC Geriatr. 2019;19(1):184). I acknowledge it would be difficult if not impossible and likely inappropriate to attempt to do this. Revisions have been made that added Kidd et al reference to manuscript and compared to our review for novelty (also a CMAJ Statistician comment).</p> <p>A general issue I had with the submission is the lack of precision and specification. The only requirement for the identification of frailty was use of a "... frailty tool, assessment of frailty, or other established criteria" (page 9 of 87), which raises the concern that they might be grouping apples and oranges. As a minimum there should have been a sub-group analysis to determine if the manner frailty was conceptualized influenced the results seen. This would have been relatively easy to do as there was a dominant approach taken in most of the included studies (see below). I also felt the nutritional interventions being considered were arguably too broad ("... food supplementation, meal programs, education, and others", page 9 of 87) while what was meant by a "physical activity" intervention was unstated (though information on this is provided in the Results section). Finally, the outcomes examined were similarly broad (i.e., a variety of outcomes fitted into eight categories including health, physical, QoL, health service use, frailty,</p>

mobility, diet quality, and one described as “social/caregiver”, which is unclear to me as to what this signifies). While I didn’t view the categories or the items within the categories as equivalent, this possibly would be fine but I would have selected a primary (or co-primary) outcome out of this list or possibly look at a composite one. The examination of the literature was up to July 2019. I think this is sufficient. I had no other pressing concerns relating to study methods.

In regards to the outcomes, we wanted to be as broad as possible as there is no established consensus as to what the most important outcomes are in this patient population. We briefly highlighted the process that we went through to select the outcomes chosen in the manuscript and have provided more details in our response here. A more fulsome list of outcomes was developed by an interdisciplinary steering committee. This thorough and detailed list was subsequently voted upon anonymously by members of this group. The rankings were then averaged and all outcomes ranked as critical were extracted and analyzed.

While we appreciate the suggestion for a subanalysis based on how frailty was conceptualized, we had originally considered this but felt it wasn’t appropriate for the following reasons. Studies used the tools in various ways and the criteria was modified across studies. We felt this analysis was not relevant if the tools were not applied consistently in different studies.

Additionally, it departs from the focus of the review as it would answer a question related to which tool is most valid for different outcomes.

Therefore, we have still chosen to not do this analysis.

Regarding the broadness of nutrition interventions, our inclusion criteria was selective for a frail population (studies which used frail definition or tool), but were not limited to one type or format of nutrition interventions. We were as inclusive as possible to reflect the diversity in strategies that have been trialed over time.

The Steering committee defined PA as “any bodily movement by skeletal muscles that results in energy expenditure above resting levels. Includes various patterns, frequencies, durations, intensities, and types.” This has been added to the manuscript.

Data Synthesis: It appears no effort was made to estimate the clinical relevance of any impacts detected. Statistical changes but not clinical relevance were looked for using SMDs (continuous variables) and RRs (dichotomous variables).

While noted as an important consideration, our group does not feel we can make specific recommendations for clinical significance. There was a lack of consistency in reporting outcomes and data from studies. In addition, there was variation in frailty tools, outcomes reported and units, etc. That is a limitation of this review and reality of the science. We are suggesting a next step for this research could be specific interventions on those with greatest input or impact. We have added this commentary to the implications section of the manuscript.

Unfortunately, conducting clinical significance analysis is not within scope for this paper, nor is it feasible as outcomes used different measures and units which were not consistent across studies. This makes it difficult to translate or transform these heterogeneous measurements into gold standard outcomes (which are not currently defined) or select one outcome from the list to inform clinical significance. The primary reason to use SMDs using Cohen’s D approach is not only to standardize the effect estimates, but also to standardize their interpretation such that we do not only say if

the effect was significant, but also quantify the magnitude of the effect (small, medium, or large). This interpretation of the magnitude of the effect can still inform clinical relevance. We have added some commentary of clinical relevance to our discussion section of the manuscript.

Data Synthesis: There is clearly a risk here of publication bias, as all studies were small (250 or fewer participants) and were published over a span of nearly two decades. One way to mitigate this (looking at unpublished literature and the grey literature) was not utilized by the authors. They state they did a funnel plot but this was not reported on.

Overall funnel plots have been completed and added to the Appendix as 10 studies (minimum) are needed for valid estimates of publication bias (reference provided in manuscript from Cochrane's handbook).

Results: I'm unclear whether one of the Tieland studies included (JAMDA 2012, 13: 713-19) met their inclusion/ exclusion criteria. On page 9 of 87 the authors state that the studies include "... had to have a true control group defined as usual care, routine care, or minimal contact which did not include any intervention or treatment group components" but in this study both arms were in a resistance-type exercise program. Whether this study is eligible or not is confused later on when the authors state, "Combined approach studies had to include both nutrition and physical activity components in the same intervention that were not standardized between groups", which might indicate the study would be eligible. I think this can be cleared up by a careful re-wording of this section or by eliminating this study.

Thank you for noting the wording in the "eligibility criteria" section. We have revised it to ensure clarity of the included studies and inclusion criteria.

Results: The sentence on page 10 of 87 ("The 2 most common tools used to measure frailty status in the participants were Fried's Frailty phenotype (36) and the Cardiovascular Health Study Criteria (36)") appears nonsensical as they are the same approach (the look for the presence of five criteria [unintentional weight loss, weakness, exhaustion, slow gait, low physical activity]with frailty present if 3+ are present). Is something missing or am I missing something? In any event the Fried Frailty/ Cardiovascular Health Study phenotype (which is more properly called physical frailty) was utilized in 11/15 (nearly three-quarters) studies included. I think it would have been possible to have done a sub-group analysis restricted to these studies.

This has been addressed in previous comments from reviewer 1 and the sub-group analysis will be addressed in a previous comment from this reviewer.

Interpretation: I'm less convinced than the authors about their conclusion that there is "moderate level evidence that nutrition, protein supplementation, and combined approach interventions are beneficial for certain components of frailty" in light of the concerns listed above and the additional limitations noted by the authors such as the short duration of most of the included studies.

"Moderate level evidence" comes from the GRADE rating of the statistically significant outcomes (which were all Moderate certainty of evidence). Slight change in wording has been updated in abstract and the limitations section and discussion of the manuscript has been heavily edited.

References: There are problems here. The study by Latham et al (Latham NK,

Anderson CS, Lee A, et al. A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in Elderly Subjects (FITNESS). J Am Geriatr Soc. 2003;51(3):291-299) is mentioned in Table 1 and 3 plus page 48 but does not appear in the list of references. Reference #28 (Eichler S, Salzwedel A, Harnath A, Nothroff J, Butter C, Schikora M, et al. Frailty as a predictor for all-cause mortality in patients 12 months after transcatheter aortic valve implantation (TAVI). European journal of preventive cardiology Conference: euoprevent 2017 Spain. 2017;24(1 Supplement 1):S150) does not appear in Tables 1, 2 or 3 (or elsewhere in the document) and doesn't seem to fit. The authors listed for reference #36 ("Fried LPea") is incomplete and incorrect. The entire list of references has to be re-checked as well as the paper itself (though I only noticed a few minor typos).

Thank you for noticing the error in the references. Reference #28 was incorrectly added and was supposed to be the Latham reference. This has been corrected. Reference #36 has also been updated and the full reference list has been reviewed and checked for completeness and accuracy.