

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The effect of physical activity and dietary restriction interventions on weight loss and the musculoskeletal function of overweight and obese elders with knee osteoarthritis: a systematic review and mixed method data synthesis
<b>AUTHORS</b>	Alrushud, Asma; Rushton, Alison; Kanavaki, Archontissa; Greig, Carolyn

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Jillian Eyles University of Sydney, Australia
<b>REVIEW RETURNED</b>	14-Nov-2016

<b>GENERAL COMMENTS</b>	<p>The effect of physical activity and dietary restriction interventions on the musculoskeletal function of overweight and obese elders with knee osteoarthritis: a systematic review and mixed method data synthesis</p> <p>bmjopen-2016-014537 Authors: Alrushud, Asma (contact); Rushton, Alison; Kanavaki, Archontissa; Greig, Carolyn</p> <p>Overall comments: This is an important topic for research and should be helpful for the body of OA research, however at the moment the manuscript needs some work to clarify the aims of the authors. I found the definition of 'musculoskeletal function' to be unclear which is the primary outcome along with weight &amp; BMI. Better definition of what musculoskeletal function entails is needed-particularly whether self-reported function &amp; functional performance measures are included. It seemed that body weight &amp; BMI were treated as primary outcomes &amp; secondary outcomes in different parts of the manuscript. Some parts of the manuscript were clear, some not so clear. I have made some detailed feedback for you to consider.</p> <p><b>ABSTRACT:</b></p> <ol style="list-style-type: none"> <li>1. The primary outcomes for the study are body weight, BMI, or musculoskeletal function but the title &amp; objective do not mention body weight or BMI. I would suggest that it would be helpful to add weight loss into the title if this is a primary outcome. Furthermore-bodyweight &amp; BMI are listed as primary outcomes in methods section of the paper but in results are secondary or other. You need to decide if body weight &amp; BMI are primary or secondary and stick to it.</li> <li>2. '(6 min walk test) at 6 months and the pooled random effect 15.05 (95% CI -11.77 to 41.87) across 2 trials with n=155 participants did not support the combined intervention...' Why? Does this random effect mean 15m difference from baseline? Or does this mean something else? If this is considered a clinically unimportant result it would be good to point this out.</li> <li>3. 'Narrative synthesis identified had higher scores for both body</li> </ol>
-------------------------	--

	<p>weight and the 6 minute walk test in the intervention groups.’ Suggest you tweak this sentence so it makes more sense 4. ‘There was moderate evidence of no effect of the combined intervention programme on mobility,’ This is not specific enough- needs to refer to 6MWT if that is the result you are referring to 5. ‘The quality of evidence of benefit of combining exercise and dietary interventions in older overweight/ obese adults with knee OA is unclear.’ I would replace with ‘evidence for benefit’</p> <p><b>INTRODUCTION:</b> 1. There are probably more current &amp; relevant references that could be used for the burden of OA for the international audience of this journal eg. Vos, T., et al., Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet, 2013. 380(9859): p. 2163-96. 2. ‘Moreover, OA is the fourth predicted cause of women’s health problems.’ This statement is a little left-field as this article does not focus specifically on women- and there is no ref for it.<sup>32</sup> ‘Unfortunately there is no specific treatment for knee OA’. Need to clarify this- there are certainly many treatments for OA- did you mean that OA is incurable? 3. The introduction gets a bit confusing with a summary of the literature that runs together without making the points of your argument clear.</p> <p><b>METHODS:</b> 1. Eligibility line 39: need to state these grades are Kellgren Laurence here 2. I would be careful about labeling advice as non-intervention care, can you call it something else? Advice is still an intervention. Do you mean instead an active vs a passive treatment 3. I feel like you haven’t explained musculoskeletal function adequately- eg can this include self-reported outcomes such as WOMAC/KOOS? And you have not mentioned functional performance measures (which is what you look at in the end with the 6MWT metaanalysis) 4. Line 26 usually need more detail about endnote version etc 5. Summary measures ‘Summary measures ‘Following data extraction, meta-analysis was possible for one key outcome measure across trials that applied similar interventions and compared with exercise at one assessment timepoint (6 months). ‘ this probably belongs in the results section, same with lines 23-24 under synthesis of results. 6. Under ‘Additional analyses’ the first sentence does not make sense (starting line 51). The rest of this section is very clear but is probably too much detail &amp; needs to be broken up a bit- is a very long paragraph</p> <p><b>RESULTS:</b> 1. Secondary &amp; additional outcomes is just a list of outcomes without referring to where they came from which is not helpful Because the primary outcomes were unclear from the start, it made interpretation of the results quite difficult. I think this will be improved once the methods section is reviewed &amp; clarified.</p> <p><b>DISCUSSION:</b> I would remove the section on cost-effectiveness as you are not looking at this in your review</p> <p><b>CONCLUSION:</b> This does not match your conclusion in your abstract. There is also a contradiction in stating ‘This systematic review has</p>
--	---

	shown that, based on current evidence from trials, a combined programme of diet and physical activity is not effective...' but then 'Only moderate quality evidence was available to investigate the intervention programmes.' Please reconsider your conclusion.
--	--

<b>REVIEWER</b>	Dr. Dinesh Bhatia Department of Biomedical Engineering, North Eastern Hill University (NEHU), Shillong-793022, Meghalaya, India
<b>REVIEW RETURNED</b>	11-Dec-2016

<b>GENERAL COMMENTS</b>	<p>Pros:</p> <ol style="list-style-type: none"> <li>1. An intensive review has been done</li> <li>2. Efficient selection presented</li> </ol> <p>Limitations:</p> <ol style="list-style-type: none"> <li>1. The study population is limited to US and UK</li> <li>2. Relevant references to be included and used accordingly</li> </ol>
-------------------------	---

<b>REVIEWER</b>	David Walsh University of Nottingham United Kingdom
<b>REVIEW RETURNED</b>	23-Dec-2016

<b>GENERAL COMMENTS</b>	<p>This systematic review has identified a paucity of data on combined exercise and dietary restriction for knee OA. The authors only identified 2 full RCTs, and were only able to undertake meta-analysis on one outcome, the 6 minute walk test which is not a functional outcome (in that forced walking distance is not an appropriate functional goal). The conclusions should be tempered given that there is more extensive evidence for the individual interventions, and no evidence or theoretical rationale presented that combining the interventions should be any worse than either intervention alone. The conclusion that 'combined programme of diet and physical activity is not effective with respect to an improvement in body weight, BMI and musculoskeletal function' is not justified by these data. Advice to combine these interventions is therefore based on sounder evidence (for the individual interventions) than is suggested by the discussion. Combination therapies should ideally be tested against each component alone, as well as against double placebo. The paucity of evidence makes any conclusions from this review somewhat speculative. None the less, the review has followed the predeclared protocol and the gaps in the evidence are of some interest in terms of designing future studies. It would benefit from being updated to include any evidence published during 2016. The depth of critique is of some value, and goes beyond, and at greater length than, that immediately evident from the 3 original research papers that are reviewed.</p>
-------------------------	--

## VERSION 1 – AUTHOR RESPONSE

### Reviewer #1

We thank the Reviewer for their positive comments highlighting the importance of this work and their generous comments about the review.

Overall comments: This is an important topic for research and should be helpful for the body of OA research, however at the moment the manuscript needs some work to clarify the aims of the authors. I found the definition of 'musculoskeletal function' to be unclear which is the primary outcome along with weight & BMI. Better definition of what musculoskeletal function entails is needed- particularly whether self-reported function & functional performance measures are included. It seemed that body weight & BMI were treated as primary outcomes & secondary outcomes in different parts of the manuscript. Some parts of the manuscript were clear, some not so clear. I have made some detailed feedback for you to consider.

We thank the Reviewer for their detailed and helpful feedback on these points which we have addressed below with respect to the appropriate section of the manuscript.

### Abstract comments:

1. The primary outcomes for the study are body weight, BMI, or musculoskeletal function but the title & objective do not mention body weight or BMI. I would suggest that it would be helpful to add weight loss into the title if this is a primary outcome. Furthermore- bodyweight & BMI are listed as primary outcomes in methods section of the paper but in results are secondary or other. You need to decide if body weight & BMI are primary or secondary and stick to it.

We agree with the Reviewer that we did not clarify sufficiently the primary and secondary outcomes in the main body of the text. We stated body weight and BMI as primary outcome measures in our protocol but the included eligible studies either did not specify them as a primary outcome or listed them as secondary outcome measures. Given that eligible studies were few in number we decided to maintain the focus on body weight and BMI as well as musculoskeletal function, i.e., data analysis was on the basis of outcomes as specified in the review but irrespective of whether they were primary or secondary in the studies we identified. We have added 'weight loss' to the title in addition to including an explanatory sentence in the Results section (lines 406-408).

2. '(6 min walk test) at 6 months and the pooled random effect 15.05 (95% CI -11.77 to 41.87) across 2 trials with n=155 participants did not support the combined intervention...' Why? Does this random effect mean 15m difference from baseline? Or does this mean something else? If this is considered a clinically unimportant result it would be good to point this out.

We consider that this result did not support the combined intervention program due to the confidence interval of the differences (CI -11.77 to 41, 87). Also, based on previous literature we do not consider a 15 metre difference to be clinically significant; as examples, Gremeaux et al., (2011) in patients with coronary heart disease report 25m as the minimal clinical difference and Perera et al., (2006) report 50m in community living older adults and people who survive a stroke . See also <http://www.rheumatology.org/I-Am-A/Rheumatologist/Research/Clinician-Researchers/Six-Minute-Walk-Test-SMWT>

The Discussion section now includes a phrase highlighting this point (see lines 567 -569).

3. 'Narrative synthesis identified had higher scores for both body weight and the 6 minute walk test in the intervention groups.' Suggest you tweak this sentence so it makes more sense

This sentence has been amended to read to "Narrative synthesis showed clear differences in favour of a reduced body weight and an increased 6 minute walk in the intervention group compared with control groups" (lines 67-69).

4. 'There was moderate evidence of no effect of the combined intervention programme on mobility,' This is not specific enough- needs to refer to 6MWT if that is the result you are referring to We prefer to delete this sentence from abstract section (line 75-77) as it related more to results rather

than the conclusion.

5. 'The quality of evidence of benefit of combining exercise and dietary interventions in older overweight/ obese adults with knee OA is unclear.' I would replace with 'evidence for benefit' We agree; this sentence has been amended (lines 73-74).

#### Introduction Comments:

1. There are probably more current & relevant references that could be used for the burden of OA for the international audience of this journal eg. Vos, T., et al., Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 2013. 380(9859): p. 2163-96.

We would like to thank the Reviewer for the helpful and valuable reference which we have included and used to present the global incidence of knee OA in older adults (lines 108-109).

2. 'Moreover, OA is the fourth predicted cause of women's health problems.' This statement is a little left-field as this article does not focus specifically on women- and there is no ref for it.32.

'Unfortunately there is no specific treatment for knee OA'. Need to clarify this- there are certainly many treatments for OA- did you mean that OA is incurable?

We agree with the Reviewer that the focus of this review was not specifically women's health. "OA is the fourth predicted cause of women's health problems" has thus been deleted (line 110).

"There is no specific treatment for knee OA" line 118 we mean the options of knee OA treatment are different and each patient may receive a different plan of intervention. We feel that this is sufficiently clear as it stands.

3. The introduction gets a bit confusing with a summary of the literature that runs together without making the points of your argument clear.

We agree with the Reviewer that we gave some details of literature that may distract the reader from the main points of argument. We have therefore deleted some details of a cited systematic review, i.e., "The risk of bias of included RCTs was assessed using the Jadad score (an instrument designed to measure the possibility of bias, scoring 0 to 5 with low scores indicating high possibility of bias) [14, 15]. The review authors assessed all trials as moderate risk of bias, with 3 RCTs scoring 3 and 2 RCTs scoring 2 [14]. The pooled effect sizes were 0.20 (95% CI 0 to 0.39) and 0.23 (0.04 to 0.42) for pain and physical disability respectively with a weight reduction of 6.1kg (4.7 to 7.6 kg)" (see lines 132 138).

Also, we have added five studies published in 2016 (reference # 7, 16, 17, 25 & 26) to support our argument. Thus the amended Introduction includes, sequentially, arthritis, knee OA incidence, knee OA management, important recommendations about exercise and body weight reduction and finally, highlights the need to investigate the effectiveness of a combined intervention programme by conducting a systematic review we have amended the reference section accordingly.

#### Methods Comments:

1. Eligibility line 39: need to state these grades are Kellgren Laurence here added line.

We have added Kellgren Laurence to knee OA grade "according to the Kellgren and Lawrence system for knee OA classification" (line 184-185).

2. I would be careful about labeling advice as non-intervention care, can you call it something else? Advice is still an intervention. Do you mean instead an active vs a passive treatment

We agree with the Reviewer that advice is a part of patient education and should be considered as an intervention. We have amended the manuscript lines 193-194 so the comparator is "Usual care

(including advice or physical activity alone or dietary restriction alone) or exercise”.

3. I feel like you haven't explained musculoskeletal function adequately- eg can this include self-reported outcomes such as WOMAC/KOOS? And you have not mentioned functional performance measures (which is what you look at in the end with the 6MWT metaanalysis)

We agree with the Reviewer that the outcome measures and our definition of musculoskeletal function were not sufficiently clear and have amended the manuscript methods section (lines 199-200) to clarify that musculoskeletal function included both self-reported function and objective functional performance measures. Also we have clarified that our indicators of musculoskeletal function were mobility, knee ROM and muscle strength.

4. Line 26 usually need more detail about endnote version etc

We have amended the manuscript line 220 to read Endnote X7.

5. Summary measures 'Summary measures

'Following data extraction, meta-analysis was possible for one key outcome measure across trials that applied similar interventions and compared with exercise at one assessment timepoint (6 months). ' this probably belongs in the results section, same with lines 23-24 under synthesis of results.

We thank the Reviewer for this comment but prefer to keep these sentences in both sections for purposes of clarity.

6. Under 'Additional analyses' the first sentence does not make sense (starting line 51). The rest of this section is very clear but is probably too much detail & needs to be broken up a bit- is a very long paragraph

We agree that this paragraph is rather long. We have amended the manuscript to clarify the meaning of the first sentence and have broken up the paragraph into 4 shorter paragraphs (but have maintained the level of detail which we feel is necessary). The first paragraph introduces the GRADE components, the second describes the first 3 components (risk of assessment tool, inconsistency and indirectness). The third describes imprecision and the final paragraph describes the publication of bias component (lines 297 - 334).

Results comments:

1. Secondary & additional outcomes is just a list of outcomes without referring to where they came from which is not helpful. Because the primary outcomes were unclear from the start, it made interpretation of the results quite difficult. I think this will be improved once the methods section is reviewed & clarified.

In the methods section we have clarified primary and secondary outcome measures. The primary outcome measures are body weight, BMI and musculoskeletal function (mobility, ROM, strength) and secondary outcome measures are pain and QoL. In the results section we have clarified that our analysis was based upon our a priori protocol listed primary and secondary outcomes. We have deleted the secondary and additional outcomes in the results section (line 422-428) and listed the primary and secondary outcomes of each included study (lines 410-421). When we analysed our findings we used a mixed method of data synthesis (meta-analysis and narrative syntheses). Meta-analysis was available for only the 6 min walk data. In the narrative synthesis we presented data according to the primary and secondary outcome measures. We have listed all the reported outcome measures which we extracted from the included trials but not possible for meta-analysis; body weight, knee ROM, physical function, mobility, pain and QoL ( lines 465-467 and 494-496).

Also, figure 1 and 2 have been removed from the manuscript and the figure legends have been included at the end of the main document.

Discussion comment:

I would remove the section on cost-effectiveness as you are not looking at this in your review

We agree with reviewer that we were not seeking data for cost-effectiveness. The manuscript has been amended accordingly, (paragraph starting line 595-606 has been removed).

In the discussion section we added a sentence about BMI (line 563-564) "Changes in BMI scores were not reported in the included studies".

Conclusion comment:

This does not match your conclusion in your abstract.

There is also a contradiction in stating 'This systematic review has shown that, based on current evidence from trials, a combined programme of diet and physical activity is not effective...' but then 'Only moderate quality evidence was available to investigate the intervention programmes.'

Please reconsider your conclusion.

The conclusion has been modified (lines 636-646) to "Based on current evidence synthesised in this review, it is hard to judge the effectiveness of a combined programme of diet and physical activity due to the low number of included trials and participants and the quality of available evidence. Only moderate quality evidence was available to investigate the intervention programmes. However, the narrative synthesis suggests that interventions with a focus on reduction of body weight and/or improved mobility are worthy of further evaluation. Further adequately powered RCT testing the effects of a combined intervention against each component individually are required to optimise diet and exercise interventions using a multimodal approach".

Reviewer: 2

We thank the Reviewer for their positive comments highlighting the strength of this work

Comment: the study population is limited to US and UK

We limited our search to English language due to limited resources. Nonetheless, we expected to identify more studies from a diverse number of countries worldwide. Unfortunately we found only 2 eligible trials and one pilot study by one research group from the USA.

Comment: relevant references to be included and used accordingly

We thank the Reviewer for their advice. A number of recent references (published in 2016) have been cited in the introduction section and included in the bibliography: Yusuf E. Pharmacologic and Non-Pharmacologic Treatment of Osteoarthritis. *Current Treatment Options in Rheumatology*. 2016 Jun 1;2(2):111-25, Hammerich AS, Anemaet WK. Applying the Evidence for Exercise Prescription in Older Adults with Knee Osteoarthritis. *Current Geriatrics Reports*. 2016 Sep 1;5(3):179-90 and Marks R. Knee Osteoarthritis, Obesity and Exercise Therapy-A Complex Issue. *J Obes Eat Disord*. 2016;2(2).

Reviewer: 3

We thank the Reviewer for their valuable comments

Comment: this systematic review has identified a paucity of data on combined exercise and dietary restriction for knee OA. The authors only identified 2 full RCTs, and were only able to undertake meta-analysis on one outcome, the 6 minute walk test which is not a functional outcome (in that forced walking distance is not an appropriate functional goal).

The conclusions should be tempered given that there is more extensive evidence for the individual interventions, and no evidence or theoretical rationale presented that combining the interventions should be any worse than either intervention alone. The conclusion that 'combined programme of diet

and physical activity is not effective with respect to an improvement in body weight, BMI and musculoskeletal function' is not justified by these data. Advice to combine these interventions is therefore based on sounder evidence (for the individual interventions) than is suggested by the discussion. Combination therapies should ideally be tested against each component alone, as well as against double placebo. The paucity of evidence makes any conclusions from this review somewhat speculative.

None the less, the review has followed the pre-declared protocol and the gaps in the evidence are of some interest in terms of designing future studies. It would benefit from being updated to include any evidence published during 2016. The depth of critique is of some value, and goes beyond, and at greater length than, that immediately evident from the 3 original research papers that are reviewed. We acknowledge the Reviewers comments about the conclusions (Reviewer 1 also makes a similar comment). To reiterate, we have modified the conclusions sections of both the abstract (lines 73-77) and the main body of the text (lines 636 – 646). In addition we have added a sentence in the conclusion in the main text about the optimum design of future interventions (lines 644-646). The search was updated (15th January 2017) by two independent reviewers to include evidence published in 2016 but unfortunately no additional eligible studies were identified; this is reported in the abstract line 51 and in the methods section lines 222-223. We would like to reiterate our thanks to the Reviewers for their comments and for the opportunity to improve the manuscript.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Jillian Peta Eyles Kolling Institute, University of Sydney, Australia
<b>REVIEW RETURNED</b>	07-Mar-2017

<b>GENERAL COMMENTS</b>	Congratulations on an improved manuscript. One further comment for the discussion section: Can you please define what you consider to be good compliance backed by relevant reference? At this point I am not convinced that compliance of 70% at 6 months is good. You may want to reconsider this discussion point unless you can back it up with evidence.
-------------------------	---

#### VERSION 2 – AUTHOR RESPONSE

Reviewer #1

We thank the Reviewer for their congratulations on our improved manuscript and their valuable comment for the discussion section.

One further comment for the discussion section: can you please define what you consider to be good compliance backed by relevant reference? At this point I am not convinced that compliance of 70% at 6 months is good. You may want to reconsider this discussion point unless you can back it up with evidence.

We agree with the Reviewer that adherence of 70% at 6 months (Messier et al., 2013) may not be considered as 'good' compared with a compliance of 94.7% by a diet plus exercise group in the earlier pilot study (Messier et al., 2000).

How best to define and measure adherence has been reviewed recently by Hawley-Hague et al. (2016) which highlights the confusion surrounding the definition of adherence (Hawley-Hague H, Horne M, Skelton DA, Todd C. Review of how we should define (and measure) adherence in studies examining older adults' participation in exercise classes. *BMJ open*. 2016 Jun 1;6(6):e011560). The review identified eight studies; each study defined adherence differently based on percentage of attendance thresholds: For example, in Stineman et al.,(2011) high adherence was classified as attending all sessions, whilst Sjösten et al., (2007) defined high adherence as 66.7–100% attendance

and Grove and Spier (1999) defined high adherence as the percentage of older adults who attended 90–100% of sessions.

In summary therefore, we prefer to avoid the judgment of ‘good’ and have amended the paragraph in the Discussion lines 530-537 to read “Compliance of the diet and exercise group to the exercise programme at 6 months was higher in the pilot study [44] compared with the IDEA trial [3]. In the pilot study [44] compliance (ratio of the number of exercise sessions attended to the total number of the exercise sessions prescribed with the exercise programme) was 82.6% for the exercise group and 94.7% for diet plus exercise group. For the IDEA trial [3], 399/ 454 participants (88%) completed the study; compliance of the diet and exercise group was 70% at 6 months and 58% at 18 months with no adverse events and no significant differences between groups”.

We would like to reiterate our thanks to the Reviewer for their comment and for the opportunity to improve the manuscript.