

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effective SLOPE: EffectS of Lifestyle interventions in Older PEople with obesity – a systematic review and network meta-analysis protocol
AUTHORS	Torbahn, Gabriel; Schoene, Daniel; Schwingshackl, Lukas; Rücker, Gerta; Knüttel, Helge; Kemmler, W; Sieber, Cornel; Batsis, John; Villareal, Dennis; Ströbele-Benschop, Nanette; Volkert, Dorothee; Kiesswetter, Eva

VERSION 1 - REVIEW

REVIEWER	Sabrina KW Wong National Healthcare Group Polyclinics Singapore
REVIEW RETURNED	30-Mar-2020

GENERAL COMMENTS	<p>This is an interesting systematic review and the use of the network analysis will allow comparison of the multiple types of interventions in older adults with obesity. In particular, the addition of behavioural interventions would provide new insights into the effectiveness of these interventions in older adults with obesity. However, the inclusion of these behavioural interventions is challenging due to heterogenous nature of these interventions, and differences in classification of these interventions.</p> <p>Since dietary and exercise interventions are also behavioural interventions, I would like to suggest that the authors consider naming interventions without a specific dietary or exercise plan “self-management” interventions or “patient-centered” interventions, where the main aim of the intervention is in helping patients develop self-management skills, rather than adhere to a prescribed regimen.</p> <p>Comments for the various sections: Introduction The authors could highlight the difference between the issues faced by older persons with obesity as compared with younger adults. Could the authors also address the obesity paradox? [1] Page 4 Line 35: This sentence should follow the sentence in the previous paragraph. Paragraph 2 starting from line 35: Many effects of obesity have been shared in this paragraph. Could the authors explain why only a few of these outcomes have been selected for the review? Also, how were the patient factors that are</p>
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of interest in subgroup analysis selected?

Some of the outcomes appear to only be associated with sarcogenic obesity, perhaps the literature regarding sarcogenic obesity could be presented together, rather than interspersed with literature on obesity.

Page 5

Line 13 to 35: This paragraph could provide more details on the types of interventions. Types of dietary interventions, exercise interventions and types of self-management interventions.

The intervention delivery methods could also be described here, to provide support for the subgroup analysis.

Page 6:

Sentence in line 13 to 20 could be added to paragraph 2 on page

Line 37: Summary of evidence from other systematic reviews "generally agree that weight-loss interventions in older adults are safe and effective in reducing weight". Could more details be given? How are they effective? How are they safe? How many RCTs have been included in these reviews?

In line 59, it states that only 1 meta-analysis has been carried out. Do the studies referred to in line 39 include meta-analyses?

Line 46, how have existing reviews been insufficient? Were there insufficient number of studies ?

Methods

Population

Why did the inclusion criteria include mean age > 65?

Are there 2 criteria for obesity, (1) body mass and waist circumference, (2) BMI?

Page 7, line 14: Please explain if sarcogenic obesity is a subgroup of interest?

Page 7 line 22-24: What comorbidities are of interest for subgroup analysis?

Interventions

Could the authors give more details on how the interventions would be classified?

An example can be found in this network meta-analysis of behavioural interventions in patients with type 2 diabetes. [3]

If the authors decide to classify the self-management interventions using behavioural change techniques, an example can be found here [2] using behavioural change techniques proposed by Michie et al. [4]

Outcomes

The authors could consider including patient satisfaction as an additional outcome measure.

Regarding falls, It could also an outcome of interest, other than being an adverse event.

1. Hainer, V. and I. Aldhoon-Hainerová, Obesity Paradox Does Exist. *Diabetes Care*, 2013. 36(Supplement 2): p. S276.

2. Wong, S.K.W., et al., Effectiveness of self-management interventions in young adults with type 1 and 2 diabetes: a systematic review and meta-analysis. *Diabetic Medicine*, 2020. 37(2): p. 229-241.

	<p>3. Pillay, J., et al., Behavioral programs for type 2 diabetes mellitus: A systematic review and network meta-analysis. <i>Annals of Internal Medicine</i>, 2015. 163(11): p. 848-860.</p> <p>4. Michie, S., et al., The Behavior Change Technique Taxonomy (v1) of 93 Hierarchically Clustered Techniques: Building an International Consensus for the Reporting of Behavior Change Interventions. <i>Annals of Behavioral Medicine</i>, 2013. 46(1): p. 81-95.</p>
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VERSION 1 – AUTHOR RESPONSE

1. Since dietary and exercise interventions are also behavioural interventions, I would like to suggest that the authors consider naming interventions without a specific dietary or exercise plan “self-management” interventions or “patient-centered” interventions, where the main aim of the intervention is in helping patients develop self-management skills, rather than adhere to a prescribed regimen.

Response: We thank the reviewer for her helpful suggestion. Summarizing all interventions that support the improvement of self-regulation, by “self-management” will make this important point clearer. Accordingly, we have rephrased the term behavioural interventions into self-management interventions throughout the manuscript and have added the following sentence to the paragraph ‘interventions’ in the methods section (page 8):

“Finally, as recommended in obesity guidelines⁸³ we will include all self-management interventions that intend to support behaviour changes (such as motivational interviewing, social support, cognitive-therapeutic intervention).⁸⁴ This is owed to the fact that many (older) people with chronic diseases (such as diabetes or obesity) have difficulties to control intended behavioural changes (such as improving eating behaviour, increasing physical activity and decreasing sedentary time).⁸⁵ In addition, self-efficacy, self-regulation skills were found important mediators for successful weight-change.⁸⁶”

2. The authors could highlight the difference between the issues faced by older persons with obesity as compared with younger adults.

Response: We have addressed this issue in the introduction (page 5) by stating:

“Findings from younger people cannot be generalised to older people due to higher levels of multimorbidity, frailty, sarcopenia and malnutrition risk.⁴⁵ Moreover, harmful side effects of interventions aiming at weight loss have to be considered, such as reduced muscle mass⁴⁶ and bone mineral density. ⁴⁷ Thus, in older people functional decline, functional limitations as well as the risk of adverse events, such as falls and fractures may be increased.⁴⁸ Very low caloric diets may lead to an inadequate intake of nutrients and consequently to the development of malnutrition, another geriatric syndrome associated with adverse health events.⁴⁹ In addition, perceived and actual barriers differ between younger and older adults in their impact on adopting lifestyle changes.⁵⁰”

3. Could the authors also address the obesity paradox? [1]

Response: Based on the reviewers’ comment, we have added a short section (page 4) addressing the obesity paradox:

“Contrary, several cohort studies have shown a lower risk for mortality in people with obesity and specific diseases such as type 2 diabetes, coronary artery disease or serious illnesses,¹⁴⁻¹⁶ which was described as ‘obesity paradox’. While research on this controversial phenomenon is still ongoing, several hypotheses are discussed, such as collider bias or effect modification.¹⁷⁻¹⁹”

4. Page 4, Line 35: This sentence should follow the sentence in the previous paragraph.

Response: We would like to keep the structure as it is. The previous paragraph defines the involved constructs and provides epidemiological data. The following paragraph deals with the consequences of obesity and sarcopenic obesity, starting with mortality and QoL.

5. Page 4, Paragraph 2 starting from line 35: Many effects of obesity have been shared in this paragraph. Could the authors explain why only a few of these outcomes have been selected for the review? Also, how were the patient factors that are of interest in subgroup analysis selected?

Response: Most of the outcomes that are described in the introduction will be included as relevant outcomes in this review. However, as it would be a lot of information in one article, we decided to not include biomarkers and genetical polymorphisms in the current work. In the respective section of the methods, we have added a few more examples (cognition, depression) and changed the section on adverse events (page 9) to avoid misunderstandings:

“Data on the occurrence of mortality, falls, fractures, hospital admission and nursing home placement as well as for other health-related event data (e.g. hypoglycaemia, hypotension), no matter if reported as outcome or adverse event, will also be considered for the current analysis”

We have also added a sentence regarding the selection of patient characteristics for subgroup analyses in the methods section on page 13:

“Patients’ characteristics for subgroup analysis were selected based on the assumption that lifestyle interventions might work differently in people who differ in aspects like vulnerability, resilience and body composition.”

6. Some of the outcomes appear to only be associated with sarcopenic obesity, perhaps the literature regarding sarcopenic obesity could be presented together, rather than interspersed with literature on obesity.

Response: Obesity in both syndromes is operationalized the same way (either high BMI, waist circumference or percentage body fat). Therefore, in our view they cannot be separated. The outcomes are relevant to both as well and thus, we decided not separating them in different text blocks. We would like to emphasise that the respective consequences have been shown for both syndromes.

7. Page 5, Line 13 to 35: This paragraph could provide more details on the types of interventions. Types of dietary interventions, exercise interventions and types of self-management interventions. The intervention delivery methods could also be described here, to provide support for the subgroup analysis.

Response: We have now added requested information from existing evidence to the section on interventions in the introduction (page 5):

“Lifestyle interventions mainly focus on diet (e.g. calorie restriction,⁴¹ high protein diet⁴²), exercise (e.g. aerobic or resistance⁴³), self-management interventions (e.g. relapse prevention or self-monitoring techniques⁴⁴ or combined strategies that vary in treatment modality (e.g. specific content), type of delivery (e.g. level of supervision, individual vs group sessions, in person vs technology) and dose (e.g. duration, intensity).”

Furthermore, we have specified the paragraph on types of interventions in the methods section (paragraph interventions, page 7/8)

8. Page 6, Sentence in line 13 to 20 could be added to paragraph 2 on page

Response: This might be a misunderstanding. But the sentence is part of paragraph 2 on page 6.

9. Page 6, Line 37: Summary of evidence from other systematic reviews

“generally agree that weight-loss interventions in older adults are safe and effective in reducing weight”. Could more details be given? How are they effective? How are they safe? How many RCTs have been included in these reviews?

Response: Based on the reviewer’s comment we have revised the respective section and now provide more information, attempting to balance proportion of manuscript sections, word count and details:

“Several systematic reviews on obesity treatment in older adults have been published between 2006-2019⁵³⁻⁶³ including 126 publications of more than 60 distinct RCTs. Reviews however, did not

identify the same studies for inclusion due to different search strategies, databases, search dates as well as differing definitions of obesity and applying various age cut-offs. They generally agree that weight-loss interventions in older adults do not cause poor health outcomes (e.g. higher risk for mortality for those randomized to the weight-loss group) and significantly reduce weight). Further, more limited evidence demonstrates improvements in measures of physical performance, such as gait speed.”

More details are given in the following sentences:

“Combined interventions (e.g., including dietary and exercise components) are to be favoured to preserve muscle mass, bone mineral density and to improve physical performance. However, self-management strategies, which are important for long-term weight maintenance from studies in younger adults,⁶⁴ have not been separately reported and discussed in existing reviews on the management of obesity in older adults. (...).”

10. In line 59, it states that only 1 meta-analysis has been carried out. Do the studies referred to in line 39 include meta-analyses?

Response: Yes, reference 63, the only meta-analysis on this topic to date is among the reviews cited in line 39 (“The only published meta-analysis dates back to 2010,⁶³ and there is no meta-analysis available for functional outcomes in older people with obesity”).

11. Line 46, how have existing reviews been insufficient? Were there insufficient number of studies?

Response: We have revised the respective section.

“However, self-management strategies, which are important for long-term weight maintenance from studies in younger adults,⁶⁴ have not been separately reported and discussed in existing reviews on the management of obesity in older adults.”

12. Why did the inclusion criteria include mean age > 65?

Response: Previous systematic reviews often contain primary studies, with mixed populations of middle-aged and older people, which, however, must be clearly separated from each other from a gerontological/geriatric point of view. Among other issues, different functional reserves, possible concomitant diseases and potential side effects of interventions have to be considered. Lifestyles also often differ, due to retirement age around 65 in many countries. Although there is no consensus, the ‘older age’ often begins at the age of 65. We see this as a limitation of previous work as no age-appropriate recommendations can be derived for the treatment of older people that are clinically relevant. Therefore, we decided to only include studies with participants’ minimum age of 60 years in combination with a mean age of at least 65 years. To further explore the relevance of increasing age on efficacy of interventions, we plan sub-group analysis based on age groups.

13. Are there 2 criteria for obesity, (1) body mass and waist circumference, (2) BMI?

Response: There will be three criteria we consider appropriate to define obesity. To avoid misunderstandings, we have changed the respective sentences (methods section, eligibility criteria, population, page 7):

“Participants will be classified as obese if one of the following criteria is fulfilled: percentage of total body fat mass $\geq 35\%$ and $\geq 25\%$ ⁶⁷ or waist circumference of $\geq 88\text{cm}$ and $\geq 102\text{cm}$ for women and men,⁶⁸ respectively or BMI, applying the standard adult cut-off of $\geq 30\text{kg/m}^2$ since there is no consensus on age-adjusted cut-offs.⁶⁹ If proven valid, we will, however consider different cut-off values for these criteria, e.g. in Asian populations.”

14. Page 7, line 14: Please explain if sarcopenic obesity is a subgroup of interest?

Response: Yes, sarcopenic obesity is a subgroup of interest. We have acknowledged this point by adding it to the objectives in order to make clear that this counts for the entire manuscript (page 6/7):

“Therefore, we will conduct a comprehensive systematic review with network meta-analyses (NMA) of RCTs to synthesize the evidence regarding the beneficial and potentially harmful effects of different

types and modalities of lifestyle interventions, or their combinations, on physical function and obesity-related outcomes such as body composition in older adults with obesity and sarcopenic obesity.”
In addition, we had already stated in the Statistical analysis section (sub-section on sensitivity and subgroup analysis):

“We will try to conduct subgroup analyses for type of obesity (sarcopenic obesity vs obesity),[...].”

15. Page 7 line 22-24: What comorbidities are of interest for subgroup analysis?

Response: We plan subgroup analyses for patients with common co-morbidities, such as diabetes, metabolic syndrome as well as type of obesity and presence of frailty and specified this point in the methods section (methods sections, statistical analysis, sensitivity and subgroup analyses, page 13):
“We will try to conduct subgroup analyses for type of obesity (sarcopenic obesity vs obesity), intervention duration (6 months), age (75 years), sex, BMI-group (35 kg/m²) and co-morbidities, such as diabetes or metabolic syndrome and frailty status.”

16. Could the authors give more details on how the interventions would be classified?

An example can be found in this network meta-analysis of behavioural interventions in patients with type 2 diabetes. [3]

If the authors decide to classify the self-management interventions using behavioural change techniques, an example can be found here [2] using behavioural change techniques proposed by Michie et al. [4]

Response: We fully agree that the different interventions should be defined and thank the reviewer for the recommended reference. In the methods section ‘data synthesis’ we have written:

“The treatment modalities (e.g. very low caloric diet, aerobic exercise, their combination or no intervention (e.g. health counselling, healthy eating/ exercise advise)) will build the nodes of the network providing maximizing similarity within and minimizing similarity between the nodes.⁷⁹”

As we plan to further separate the nodes according to intervention characteristics, we have added the following sentences (methods sections, data synthesis, page 12):

“To further identify important determinants of efficacy and safety, nodes will be further defined, e.g. according to the duration, intensity, mode of delivery of interventions.¹⁰⁵ Based on data availability, these nodes will be defined after data extraction.”

17. The authors could consider including patient satisfaction as an additional outcome measure.

Response: We agree and we had stated this before (page 9): “[...] and satisfaction with intervention will also be captured”.

18. Regarding falls, It could also an outcome of interest, other than being an adverse event.

Response: We agree, that events such as falls are highly relevant for interventions in older people. We have now changed the sentence to acknowledge that such events might be reported as outcome as well as adverse event. It reads now (see methods section, eligibility criteria, other outcomes, page 9):

“Data on the occurrence of mortality, falls, fractures, hospital admission and nursing home placement as well as for other health-related event data (e.g. hypoglycaemia, hypotension), no matter if reported as outcome or adverse event, will also be considered for the current analysis.”