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Effective SLOPE: EffectS of Lifestyle interventions in Older PEople with obesity: a systematic review and network meta-analysis protocol

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ABSTRACT

Introduction Obesity is highly prevalent in older adults aged 65 years or older. Different lifestyle interventions (diet, exercise, self-management) are available but benefits and harms have not been fully quantified comparing all available health promotion interventions. Special consideration must be given to functional outcomes and possible adverse effects (loss of muscle and bone mass, hypoglycaemia) of weight loss interventions in this age group. The objective of this study is to synthesise the evidence regarding the 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.

Methods and analyses Six databases (Medline, Embase, Cochrane Central Register of Controlled Trials, Cumulated Index to Nursing and Allied Health Literature (CINAHL), Psychinfo and Web of Science) and two trial registries (Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform) will be searched for randomised controlled trials of lifestyle interventions in older adults with obesity. Screening (title/abstract and full-text) and data extraction of references as well as assessment of risk of bias and rating of the certainty of evidence (Grading of Recommendations, Assessment, Development and Evaluation for network meta-analyses) will be performed by two reviewers independently. Frequentist random-effects network meta-analyses will be conducted to determine the pooled effects from each intervention.

Ethics and dissemination We will submit our findings to peer-reviewed journals and present at national and international conferences as well as in scientific medical societies. Patient-targeted dissemination will involve local and national advocate groups.

PROSPERO registration number CRD42019147286.

Strengths and limitations of this study

- This will be the first network meta-analyses (NMA) on lifestyle interventions in older adults with obesity.
- Rather than focussing on weight loss, physical functioning will be the primary interest due to its subjective and objective relevance for older people.
- Methods will be applied based on the standards of the updated version 6.0 of the Cochrane Handbook for Interventions (updated July 2019).
- Recommendations will be derived based on the results according to the Grading of Recommendations, Assessment, Development and Evaluation approach for NMA.
- Heterogeneity (clinical and statistical) will be evaluated and discussed in detail.

INTRODUCTION

Obesity is defined as an abnormal and excessive accumulation of body fat,[1] while on a population level, is defined using a body mass index (BMI) ≥30 kg/m^2. Over the past four decades, the prevalence of obesity has been increasing worldwide across all age groups.[2] The rate of obesity in older adults, the fastest growing population segment,[3] have now exceeded 40%, making this a public health concern.[4] As BMI has poor sensitivity in older adults due to age-related changes in body composition and a reduction of body height,[5] waist circumference and, more directly, objectively-measured fat mass can be considered in ascertaining obesity. In the USA, central obesity measured using waist circumference has been found in ~63% of community-dwelling adults aged ≥60 years.[6] The prevalence of obesity according to a high proportion of fat mass is 64% and 77% in German women and men ≥70 years, respectively.[7 8] Due to the higher mechanical load of a higher body weight, for a long time obesity has not been linked to a low proportion of muscle mass. However, in recent years, sarcopenic obesity, a syndrome combining obesity with low muscle mass and strength or physical function, has gained considerable attention.

Sarcopenic obesity is a largely underdiagnosed condition in clinical practice, and prevalences of up to 94% in older adults depending on the operationalisation of this construct have been reported.[9]

In community-dwelling older adults, obesity and sarcopenic obesity are associated with increased mortality[10 11] as well as with reduced quality of life (QoL).[12 13] 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] Obesity is a well-known risk factor for metabolic and cardiovascular diseases, pulmonary abnormalities and certain types of cancer in older age.[20] Furthermore, obesity is associated with the onset of osteoarthritis in older adults,[21] one of the most disabling medical conditions, severely affecting one's QoL.[22] A meta-analysis of 26 prospective studies in older adults revealed obesity as risk factor for functional decline[23] which is of utmost importance for independent living.[24 25] Older adults with sarcopenic obesity are considered a group at particular risk for functional limitations as they are suffering from two conditions determining functional disability simultaneously.[26 27] Moreover, in older people obesity and sarcopenic obesity are associated with an increased risk of falls[28–31] and nursing home admissions.[32] Alley *et al* have predicted that given the increasing prevalence of obesity, a disabled older person with obesity may become the most common phenotype of frailty[33]—another syndrome in the geriatric population that is associated with decline in health and function[34 35]—posing a marked personal and societal burden. In 2015, a high BMI contributed to about 120 million disability-adjusted life years (DALYs) representing ~5% of DALYs from any causes among adults worldwide.[2] A recent systematic review found that compared with healthy weight, the total annual healthcare costs are 30% (IQR: 20%–34%) higher in middle-aged and older people with obesity.[36] An analysis of the World Obesity Foundation in 2017 has forecasted that costs of consequences of overweight and obesity will further increase in the future.[37]

Although other therapeutic options to treat obesity exist (eg, bariatric surgery), lifestyle strategies should always be first-line treatment.[38–40] Lifestyle interventions mainly focus on diet, exercise, self-management or combined strategies that vary in treatment modality (eg, specific content), type of delivery (eg, level of supervision) and dose. Lifestyle interventions mainly focus on diet (eg, calorie restriction[41]), high-protein diet,[42] exercise (eg, aerobic or resistance[43]), self-management interventions (eg, relapse prevention or self-monitoring techniques[44]) or combined strategies that vary in treatment modality (eg, specific content), type of delivery (eg, level of supervision, individual vs group sessions, in person vs technology) and dose (eg, duration, intensity). 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 mass[46] 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] Despite these issues, obesity treatment in older adults is still not sufficiently addressed in existing obesity guidelines.[39 51 52]

Several systematic reviews on obesity treatment in older adults have been published between 2006 and 2019[53–63] including 126 publications of more than 60 distinct randomised controlled trials (RCTs). These systematic 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 (eg, higher risk for mortality for those randomised to the weight-loss group and significantly reduce weight). Further, more limited evidence demonstrates improvements in measures of physical performance, such as gait speed. Combined interventions (eg, 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. In addition, methodological issues prevent the drawing of firm conclusions, for example, recommendations for obesity treatment. These include too specific searches in only one database, not covering the complete time period of databases and application of language restrictions. This must be considered insufficient as it likely missed relevant evidence.[65 66] Further, a quality rating of the included RCTs was missing in the majority of these systematic reviews or when done, some used no standardised tools. 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. Considering, recently published intervention studies, for example, Ard *et al*[67] and Beavers *et al*,[68] it is likely that accumulated evidence enables quantitative syntheses.

These limitations of existing systematic reviews highlight an evidence gap and justify the need for a thoroughly conducted high-quality systematic review according to the updated standards described by the Cochrane collaboration for network meta-analysis.[69 70] As older adults are particularly susceptible to negative effects of excess body mass on physical function due to the age-related decline

in muscle mass and strength[20] and frequently report the priority of functional outcomes related to mobility and daily life tasks,[71] these outcomes should be investigated comprehensively.

An important question remaining is which type of lifestyle intervention or treatment modality offers optimal benefits in older adults with obesity. As there exist a large number of possible interventions, multiple pairwise meta-analyses are insufficient to provide an answer of high certainty. Therefore, we will conduct a comprehensive systematic review with network meta-analyses (NMA) of RCTs to synthesise 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.

METHODS AND ANALYSIS

Reporting

We report this protocol according to the Preferred Reporting Items for Systematic Review and Meta-Analyses statement for systematic review protocols (PRISMA-P, see online supplemental file 1),[72] the additional guidance for NMA by Chaimani *et al*[73] and the guidance for systematic reviews of older adults by Shenkin *et al*[74] to ensure thorough reporting and implementation. The methodology is preregistered on the International Prospective Register of Systematic Reviews (registration number CRD42019147286).[75]

Eligibility criteria

We will select primary studies according to the criteria below.

Population

To focus this systematic review on older adults, we will include studies including adults with a minimum age of 60 years and a mean of ≥65 years.[76] Participants will be classified as obese if one of the following criteria is fulfilled: percentage of total body fat mass ≥35% and ≥25%[77] or waist circumference of ≥88 cm and ≥102 cm for women and men,[78] or BMI, applying the standard adult cut-off of ≥30 kg/m^2 since there is no consensus on age-adjusted cut-offs.[79] If proven valid, we will, however, consider different cut-off values for these criteria, for example, in Asian populations. For all three operationalisations, the methods of measurement applied by individual studies will be used. When studies report mixed samples of older adults with overweight and obesity, we will contact the authors to request the data for the subgroup with obesity. If the provision of data is not possible, the study will be excluded. No consensus definition of sarcopenic obesity exists and various operationalisations are in use.[9] As such, the definition applied by the primary study will be used, and we shall acknowledge differences in potential subgroup or sensitivity analyses, if possible. Due to the high prevalence of multimorbidity in older people and existing obesity-related comorbidities, participants with common comorbidities of obesity (eg, diabetes, cardiovascular disease, metabolic syndrome, chronic kidney disease, osteoarthritis and geriatric syndromes (eg, frailty and sarcopenia)) will be included. We will only include studies comprising community-dwelling older adults, due to the predictive value of obesity for nursing home admissions.[80] Studies focusing on animals, genetics or biochemistry will be excluded. References that have not been included after full-text screening will be listed in a table with the respective reason(s) for exclusion.

Interventions

We will include any type of lifestyle intervention, for example, diet, exercise, self-management, as well as all treatment modalities and their combinations with all types of deliveries and doses. For the dietary component, interventions affecting energy balance, such as energy restriction, balanced (healthy) diet (eg, food pyramid), Mediterranean diet, high-protein diet, low-fat diet, moderate-carbohydrate diet, low-carbohydrate diet, low glycaemic index/glycaemic load diet, vegetarian diet, Dietary Approaches to Stop Hypertension (DASH), will be considered. Interventions providing only micronutrient supplements (eg, vitamin D) as well as studies using only very low energy diets (<800 kcal/day) or total diet replacement will be excluded.[81] Additionally, RCTs focussing on substances such as secondary plant products (eg, polyphenols), components of macronutrients (eg, fatty (docosahexaenoic acid) or amino acids (eg, leucin)) and fibres will also be excluded. The exercise component will be defined as any planned, structured and repetitive movement with the objective to improve or maintain physical fitness, for example, aerobic, resistance, balance training, according to the definition of the American College of Sports Medicine.[82] We will also consider physically supported methods, such as electrical muscle stimulation and vibration training when combined with gross movements or done in an upright position. Finally, as recommended in obesity guidelines[83] 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]

Comparators

Since NMA will be conducted, all interventions will be compared with each other. Additionally, control groups, such as usual care or health counselling, will be considered as comparators.

Outcomes

Only previously validated outcomes will be considered and need to be measured at least preintervention and postintervention.

Main outcome

The change in *functional status* with focus on physical function was shown to be important to health and adverse outcomes[24 25] and patient-relevant[71] and will therefore be our main outcome. This includes standard measures of strength, mobility and functional performance for independence in daily living, including their modifications. Common measurements include but are not limited to one-leg stance (balance), gait speed (gait, mobility), 6 min walk test (endurance), repeated chair stands (functional strength, lower extremity function), grip strength (strength, overall function), leg power as well as composite scores of functional tests such as the short-physical-performance battery[25] or the physical performance test.[87] Patient-reported outcomes of functional status (eg, Late-Life Function and Disability Instrument) and digital measurements (eg, instrumented gait analysis)) will also be considered.

Other outcomes

To evaluate changes in *weight and body composition*, we will consider measures such as total body mass, fat mass (eg, total, central, peripheral), lean mass, muscle mass (eg, total, appendicular, lower extremity skeletal), bone mineral density (eg, hip, lumbar spine, whole body).

(Health-related) QoL will be summarised when reported by standardised instruments such as 36-item short form survey[88] or EuroQol-5D.[89] If reported in primary studies, *emotional status* (eg, depressive symptoms, depression), *social participation* (eg, informal social relationships, community life) and satisfaction with intervention will also be captured.

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

Design of primary studies

We will include (quasi-) RCTs (parallel and crossover). Due to a lower level of initial fitness, prevalent health restrictions and the time needed to respond to treatment, we will include studies with intervention durations of ≥12 weeks.[50]

We will not set any restrictions regarding language or time frame. We will involve colleagues who are fluent in the respective languages or use online translators (eg, https://www.deepl.com/home).

Conference abstracts will be excluded.

Search strategy

Six electronic databases (Medline, Embase, Cochrane Central, Cumulated Index to Nursing and Allied Health Literature (CINAHL), PsychInfo and Web of Science) for published trials and two trial registries (Clinicaltrials.gov, WHO International Clinical Trials Registry Platform) for unpublished or ongoing trials will be searched. We developed the search strategy for Medline (via Ovid) (see online supplemental file 2) using a search block for people aged ≥65 years and adapted a block for interventions from a recently published Cochrane review evaluating lifestyle interventions in paediatric patients with overweight and obesity, which was reviewed and revised by information specialists.[90] For other databases, the search strategy will be adapted according to the database-specific requirements. Additionally, we will screen reference lists of published systematic reviews and eligible RCTs for potential consideration of further primary RCTs and will contact the advisory board which consists of clinical and scientific experts to enquire whether all relevant studies were identified.

Selection process

Identified references will be saved in Endnote and after excluding duplicates, references will be uploaded to Covidence (http://www.covidence.org). Two reviewers (GT, DS) will independently screen titles/abstracts and full texts for eligibility according to the criteria described above. The title/abstract screening will be piloted using the first 200 references and in case of too many deviations (>10%), it will be revised. Disagreements will be solved by discussion or if no consensus can be reached by a third reviewer who will be asked based on his/her expertise (nutrition/general (EK), exercise (WK), self-management (NS-B)). If relevant information is lacking, we will contact the corresponding author/s twice at a weekly interval.

Data extraction

Two reviewers (GT, DS) will extract data of included references independently using a piloted data extraction table. In case of no consensus, a third reviewer (based on expertise) will solve disagreements. If relevant data are missing, we will contact the corresponding author/s twice at weekly intervals.

When extracting the data, we will consider the following information: *study characteristics*: for example, author, publication year, eligibility criteria, setting, study duration, sample size, follow-up time, conflict of interest; *participants' characteristics*: for example, age, sex, ethnicity, BMI, body composition (eg, fat mass, muscle mass, height/weight adjusted indices), comorbidities (eg, diabetes, cardiovascular disease), geriatric syndromes (eg, sarcopenia, frailty, cognitive impairment), functional status, lifestyle behaviour (eg, sedentary); *intervention characteristics*: type and modality, type of delivery, dose (eg, duration, frequency, intensity), control arms, cointerventions, compliance and adherence, drop out, (serious) adverse events related to intervention; *outcomes*: baseline values and follow-up values of functional status, BMI, weight, body composition (lean mass, fat mass), QoL, emotional

status, social participation and any reported poor health outcome as reported by study authors.

Assessment of risk of bias

The risk of bias will be assessed after a pilot trial (n=3) by two reviewers (GT, DS; not blinded to authors and journal of primary studies) independently using the revised Cochrane risk of bias tool (RoB 2.0) for RCTs.[91 92] According to this, sources of bias will be identified by assessing: (1) the randomisation process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome and (5) selection of the reported result. For each domain, available algorithms will be followed to answer the signalling questions (response options: yes, probably yes, probably no, no or no information) and to judge the risk of bias as low, some concerns, or high. The overall risk of bias will also be rated as low (if low risk of bias in all domains), some concerns (at least one domain is rated as having some concerns but no domain is rated by a high risk of bias) or high (if at least one domain is judged with a high risk of bias or multiple domains are rated as having some concerns which might impact the confidence in a result). We will present results in a risk of bias summary graph.

Assessment of certainty of evidence

Grading of Recommendations, Assessment, Development and Evaluation approach for NMA will be used to assess the certainty of evidence.[93–95] In addition to the risk of bias rating for every outcome, this includes the rating of direct and indirect evidence for inconsistency, indirectness and dissemination bias. In case of high certainty and a similar contribution of direct and indirect evidence to the network estimate, the highest rating will be used but could be further downrated for incoherence and imprecision. In case of insufficient evidence as well as moderate, low or very low certainty, the indirect estimate will be rated by the lowest of two direct comparisons included in first-order loops and could be further downrated for intransitivity. Dissemination bias will be investigated by searching for unpublished trials (see section search strategy). 'Summary of findings' tables adapted for NMA results will be presented, similar to the proposal by Yepes-Nuñez *et al*.[96]

Statistical analyses

Measures of treatment effect

Effect sizes for continuous outcomes (eg, weight loss, muscle strength) will be expressed as mean difference or standardised mean difference with 95% CI. For dichotomous outcomes (eg, negative health outcome such as death), effect sizes will be expressed as risk ratios with 95% CI.[97] In exceptional cases (ie, if a minor number of RCTs expressed as negative health outcome continuously while the majority used dichotomous outcomes), the outcomes reported as continuous or categorical will be dichotomised.[98] If the postintervention values with the corresponding SD are not available, the changed scores with the corresponding SD will be used.[99]

Data synthesis

We will conduct random effects model NMA based on a frequentist approach to derive pooled estimates for all outcomes.[100] We will use the R package 'netmeta'.[101] In NMA, evidence from direct comparisons and indirect comparisons is averaged to calculate a network estimate. The key requirement for conducting NMA is that the transitivity assumption—to compare two interventions via an indirect route in the network—is ensured. We assume that for our planned analyses, all interventions are jointly randomisable[73 102] and that all participants are likely to receive any kind of included interventions. Network graphs will be generated by function *netgraph*() of netmeta.[101 103] We will assess global incoherence by decomposing the Q statistic into heterogeneity (within designs) and inconsistency (between designs) and visualise this using a net-heat plot.[104] In addition, we will report and assess inconsistency by calculating differences between direct and indirect effect estimates using descriptive z-tests (function *netsplit*()) and report the distribution of direct and indirect evidence. The treatment modalities (eg, very low caloric diet, aerobic exercise, their combination or no intervention (eg, health counselling, healthy eating/ exercise advise)) will build the nodes of the network providing maximising similarity within and minimising similarity between the nodes.[93] To further identify important determinants of efficacy and safety, nodes will be further defined, for example, according to the duration, intensity, mode of delivery of interventions.[105] Based on data availability, these nodes will be defined after data extraction. Additionally, we will analyse the components (eg, of combined interventions using an additive model for multicomponent interventions).[106] Models of this type allow disentangling the effects of all single components (eg, very low caloric diet (A), aerobic exercise (B), behavioural group counselling (C)) of a multicomponent intervention arm consisting of at least two single components (eg, A+B, A+C, B+C or A+B+C). Since we do not believe that lifestyle interventions that are available for treatment of obesity may fulfil the additivity assumption for component NMA (CNMA)—that is, the effect of a multicomponent intervention equals the sum of their components without any interactions—we will use the interaction CNMA model which is implemented in the function *netcomb*() of netmeta.[101 106] In the case of disconnected networks, we will reconnect the networks if possible (ie, presence of at least one common component in the subnetworks). This feature of CNMA is also implemented in netmeta (function *discomb*()).

A secondary data analysis will be conducted using intervention types as network nodes (eg, diet, exercise, self-management). Results of NMA will be presented as forest plots. We will present league tables containing relative treatment effects for all direct comparisons (function *netleague*()) and a ranking of all treatments by P-scores.[107]

Sensitivity and subgroup analyses

If possible, sensitivity analyses will be conducted by only including studies rated as low risk of bias. 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/m^2) and comorbidities, such as diabetes or metabolic syndrome and frailty status. 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.

Patient and public involvement

Before the start of this NMA, we have conducted and are currently analysing a qualitative study with semistructured interviews in older persons with obesity. The aim is to obtain further information on patients' motives, barriers, experiences and perceptions regarding therapeutic lifestyle interventions and thus, potentially identify evidence gaps. The results will be published in a separate manuscript.

In addition, we discuss patient-relevant outcomes, existing obstacles that exacerbate the process of contacting this population of patients as well as potential dissemination strategies with representatives of German patient advocate groups.

ETHICS AND DISSEMINATION

For NMA, there is no direct data collection from human participants and hence, no ethical approval is necessary.

We will submit our research articles to peer-reviewed journals and will present our results at national and international conferences. Involved experts will disseminate the results in scientific and medical societies. We will further disseminate our project via partner universities' websites and press releases. Patient-targeted dissemination will involve local and national advocate groups and offices for senior affairs. In addition, we will disseminate the results by distribution of materials in plain language.

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Contributors GT, DS and EK planned and designed this project, drafted the manuscript and approved the final version. LS, GR, HK, WK, CCS, JAB, DTV, NS-B, and DV were involved in the planning and design process of this project, provided critical feedback for the manuscript and approved the final version. EK will be the guarantor of the review.

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