The effects of exercise and low-calorie diets compared with low-calorie diets alone on health: a protocol for systematic reviews and meta-analyses of controlled clinical trials

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Protocol

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Abstract

Background: Exercise and weight loss diets are two independent non-pharmaceutical strategies known to improve several aspects of body composition and health. We plan to systematically review randomized controlled trials investigating weight loss diets alone compared to weight loss diets in conjunction with exercise on energy intake, body weight, body composition, cardiometabolic risk factors, sex hormones, and mental health.

Methods and analysis: PubMed/MEDLINE, EMBASE, ISI (Web of sciences), Scopus, and Google Scholar will be searched to retrieve potential controlled clinical trials investigating the effects of exercise in conjunction with weight-loss diets compared with weight-loss diets alone on energy intake, body weight and composition (fat mass, fat-free mass), anthropometrics (waist circumference), cardiometabolic markers, sex hormones [testosterone, estradiol, and sex hormone binding globulin (SHBG)], liver and kidney enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), uric acid, blood urea nitrogen (BUN), and glomerular filtration rate (GFR), quality of life, and depression in adults will be included. The weighted mean difference (WMD) and its corresponding 95% confidence intervals (CIs) will be derived using the random effects model. Several subgroup analyses such as gender, age, BMI, exercise protocol, and diet used for weight loss will be conducted to explore possible sources of heterogeneity. Publication bias will be explored by inspecting funnel plots and by conducting asymmetry tests. Overall quality of the evidence will be assessed by using the NutriGrade scoring system, which is designed to judge the overall quality of meta-analyses of clinical trials conducted in the field of nutrition.

Discussion: This proposed systematic review and meta-analysis aims to compare the effects of a low-calorie diet with low-calorie diet plus exercise on the risk factors for chronic diseases. We hope this systematic review and meta-analysis will provide valuable information regarding the values which exercise add to weight-loss diets. No primary data are going to be collected; therefore, ethical approval is not required. The resulting manuscripts will be disseminated in peer-reviewed journals and at international and local conferences.

Systematic review registration: This protocol in being considered for registration in the International Prospective Register of Systematic Reviews (PROSPERO).

Background

The worldwide prevalence of obesity and associated metabolic abnormalities has put a large strain on health care systems[1, 2]. The increase in prevalence of obesity in recent decades is multifactorial, however sedentary lifestyle and poor dietary intake are proposed to be the two major contributing factors[2, 3]. Furthermore, obesity is associated with a lower quality of life and higher risk factors for several diseases, such as metabolic syndrome, diabetes, cardiovascular disease (CVD) and cancers[4, 5].

Lifestyle modifications including changes in diet and physical activity are regarded as the main non-pharmacological and non-surgical strategies to treat obesity [6]. Modified dietary macro-nutrient intake leading to a hypocaloric diet is effective for weight loss over the short term and may be important for weight loss maintenance compared to exercise alone. Low-calorie diets not only reduce body weight but also improve cardiometabolic health, quality of life, and even mental health[7–14]; however, it is proposed that weight-loss diets might adversely affect bone health in adults[15]. It is also plausible that exercise may alter energy balance and influence body weight and health over time. Despite, the well-known benefits of exercise, the increase in energy expenditure[17] and the potential to decrease hunger and energy intake[18], exercise alone does not seem to be effective at altering weight[16, 17]. Beyond weight-loss, exercise, may modulate metabolism and lead to an increase in muscle mass[18–21]. Furthermore, exercise (particularly weight bearing exercise) may be effective at enhancing bone health[15].

In theory, exercise in conjunction with weight loss diets may be ideal to improve weight-loss as well as appetite, body composition, cardiovascular health, and mental health[22–24]. However, controlled clinical trials have led to inconsistent results[25–29], with some studies demonstrating no additive effect of exercise[25, 26] while others found a greater effect with exercise for improving multiple cardiometabolic risk factors in obese adults[27, 28]. A number of clinical trials have revealed that subjects show a significant weight loss and reduction in energy intake during an exercise intervention while others have shown less reduction in body weight due to an increase in the energy intake [30–32]. These conflicting results were also observed on other health outcomes such as, bone health, appetite, and mood[33–37].

Although the effects of exercise programs and weight-loss diets are well investigated, we are not aware of any systematic review attempting to summarize the current evidence regarding the additive impact of exercise combined with weight loss diets on cardiovascular, mental, and bone health, as well as body composition changes over time. Meta-analyses will be done when sufficient trials are available for each outcome variable, including energy intake, body weight and composition, anthropometric measures, cardiometabolic markers, bone health markers, sex hormones, liver and kidney enzymes, quality of life, and depression in adults.

Methods

The reporting will be in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for protocols (PRISMA-P)[38].

Search strategy

The relevant articles will be identified in the following databases up to 30 Sep 2019: PubMed/MEDLINE, EMBASE, ISI (Web of sciences), Scopus, and Google Scholar. We will not apply any language or other restrictions to search the databases. In addition, we will check the reference lists of all relevant studies to identify additional relevant articles through manual search. The search strategies that will be applied in different databases are provided in *Supplementary table 1.*

Study selection

Two investigators will independently perform the study selection. All articles from electronic searches will be imported into the EndNote software (version: desktop, X7; Thompson Reuters, New York, USA), then duplicate studies will be deleted. Titles, abstracts and full-text articles will be screened and also cross-checked according to the eligibility criteria for study inclusion independently by 6 reviewers (Z.Y, S.S, S.B, SH.R, S.MT, and T.Z). Any disagreements will be resolved by discussion and consensus. The PRISMA flow chart will be presented to describe the process of the study selection. Articles will be selected for full text review is they meet the following criteria: (i) participants must be 18 years of age and higher and have a body mass index(BMI) $\geq$ 25 kg/m^2 (pregnant and lactating women will be excluded); (ii) interventions must contain one arm in which participants receive an exercise intervention (i.e. aerobic or resistance) with a weight-loss (i.e. hypocaloric) diet and one arm where participants only receive a weight loss diet; (iii) interventions must be controlled clinical trials with either a parallel or cross-over design with at least two weeks of follow-up and (iv) include energy intake, body weight, body composition, cardiovascular disease (CVD) risk factors (including blood glucose control markers, lipid profile, blood pressure), serum inflammatory markers, serum oxidative stress markers, sexual hormones status, bone health, quality of life, anxiety, or depression measures.

Data Extraction

Data extraction and management

The following data will be extracted by two independent investigators from the eligible studies and any discrepancy will be resolved by contacting a third author:

Study and participant's characteristics: The participants' age, sex, number of males and females, number of participants in the intervention and control group/period, the geographical location of the study and the health condition of participants.

Intervention details: The study design (parallel/cross-over/etc.), geographic region in which the studies were conducted, number of study arms, the intervention duration, funding source(s), amount of calorie restriction, type of diets, and the exercise program used for the intervention group.

Outcome measures: Data on baseline, post-intervention or change from baseline mean ± standard deviation (SD) for energy intake, anthropometric measures, blood glucose control markers (serum/plasma fasting glucose, insulin, C-peptide, insulin resistance markers including HOMA-IR and hemoglobin A1C), lipid profile [serum total cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and apoproteins], systolic and diastolic blood pressure, sexual hormones (testosterone and estradiol), SHBG, serum/plasma inflammation (hs_CRP, IL_6, and TNF_a), depression, anxiety and quality of life, will be extracted for the intervention and control

groups/periods. P-values for within-group and between-group comparison will also be collected to calculate the change values.

Assessment of risk of bias in individual studies

The eligible studies will be assessed using the Cochrane collaboration's risk of bias assessment tool considering 7 domains: (i) random sequence generation (selection bias), (ii) allocation concealment (selection bias), (iii) blinding of participants and personnel (performance bias), (iv) blinding of outcome assessment (detection bias), (v) incomplete outcome data (attrition bias), (vi) selective reporting (reporting bias), and (vii) the dietary compliance as another possible source of bias in dietary interventions. Each study will be judged as low risk of bias, high risk of bias, or unclear risk of bias according to the mentioned domains[39]. As blinding of the participants and personnel is not possible in clinical trials examining the effect of diet and exercise, we will consider the remaining domains (random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and dietary compliance) as key domains. The overall quality of studies will be classified as low risk (low risk for all domains), unclear risk (unclear for at least one domain), and high risk (high risk for at least one domain).

Data analysis

The mean change values from baseline for the intervention (weight loss diet + exercise) and control group/period (weight loss diet alone) and their standard deviations (SDs) will be used to calculate the raw mean difference and its standard error (SE) between the intervention and control groups/periods. The hedges' g (bias corrected standardized mean difference) statistic and its corresponding SD will be calculated for outcome variables reported in different scales. The mean difference will be used as the effect size for meta-analysis. If the change values were not reported, we will calculate SD for the change values by selecting 0.5 as the reference correlation coefficient between baseline and end line values ($r = 0.5$) and to make sure that the meta-analysis was not sensitive to the selected correlation coefficient, all analyses will be repeated by the use of 0.2 and 0.8 as correlation coefficient. The weighted mean difference (WMD) and its corresponding 95% confidence intervals (CIs) will be derived by using the random effects model which takes the between-study heterogeneity into account[40]. All statistical analyses were performed using STATA, version 11.2 (Stata Corp, College Station, TX) and two-sided P-values less than 0.05 will be considered as statistically significant.

Between study heterogeneity and subgroup analysis

The heterogeneity will be checked by using the Cochran's Q test and I-squared statistic (I^2 is an estimate for between study variation to total meta-analysis variation ratio ranging from 0–100%,)[41]. P values less than 0.05 for Cochran's Q test and $I^2 \geq 25\%$ will be considered as high level of heterogeneity. To

examine the potential sources of between-study heterogeneity, several subgroup analyses based on follow-up duration, the health status of the participants, the diet used for weight loss, the exercise used for intervention, participants' sex and other possible variables will be conducted.

Sensitivity analysis

The sensitivity analysis will be done by sequential removing individual studies included in meta-analyses to assess the robustness of the meta-analyses[42].

Publication bias

Publication bias will be evaluated by inspecting Begg's funnel plots and Egger's and Begg's asymmetry tests[43]. Duval and Tweedie's trim and fill analysis will be conducted if the publication bias becomes evident[44].

Dealing with missing data

If necessary data are missing, we will attempt to contact the authors through e-mails to obtain missing data or additional information twice, one week apart. The impact of missing data will also be evaluated in the sensitivity analysis. Additionally, we will describe the possible influences of missing data in the "Discussion" section of the resulting publications.

Confidence in cumulative evidence

The overall quality of the meta-evidence will be assessed by using the NutriGrade scoring system, which is designed to judge the overall quality of meta-analyses of clinical trials conducted in the field of nutrition. NutriGrade considers the risk of bias/study quality/study limitations (3 points), precision (1 point), heterogeneity (1 point), directness (1 point), funding bias (1 point), publication bias (1 point), and study design (2 point) to rate the confidence in the provided evidence[45]. A meta-analysis will receive a maximum of 10 points. This tool suggests 4 categories for the overall quality of meta-evidence: high (≥ 8 points), moderate (6–7.99 points), low (4–5.99 points) and very low (≤ 3.99 points) confidence.

Discussion

For decades, epidemiological and clinical studies have been elucidating the link between lifestyle modifications and health outcomes through different mechanisms[46]. Previous reviews have assessed the impacts of diet or exercise alone on energy intake and different health indicators, while there is no comprehensive investigation trying to summarize the evidence evaluating the effects of weight-loss diets combined with exercise interventions on energy intake, anthropometric measurements, blood glucose control, cardio-metabolic markers and mental health.

In conclusion, this study aimed to provide a protocol for systematic review and meta-analyses to compare the effects of a low-calorie diet with a low-calorie diet plus exercise on the risk factors associated with chronic diseases. Finally, this systematic review and meta-analyses will potentially provide more information regarding the values which exercise add to weight-loss diets.

Abbreviations

SHBG: Sex Hormone Binding Globulin

ALT: Alanine Aminotransferase

AST: Aspartate Aminotransferase

GGT: Gamma-Glutamyl Transferase

BUN: Uric Acid, Blood Urea Nitrogen

GFR: Glomerular Filtration Rate

WMD: Weighted Mean Difference

CI: Confidence interval

CVD: Cardiovascular Disease

BMI: Body Mass Index

LDL-C: Low Density Lipoprotein Cholesterol

HDL-C: High Density Lipoprotein Cholesterol

hs_CRP: high sensitive C-Reactive Protein

IL–6: Interleukin 6

TNF-α: Tumor Necrosis Factor alpha

PROSPERO: International Prospective Register of Systematic Reviews

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

MESH: Medical Subject Headings

SD: Standard Deviation

SE: Standard Error

Declarations

Ethics approval and consent to participate

We will follow the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) for reporting the present systematic review and meta-analysis. The protocol is undergoing registration in the International Prospective Register of Systematic Reviews (PROSPERO) database.

Consent for publication

No individual detail is presented in this protocol; therefore, it is not applicable.

Availability of data and material

The studies included in the review will be available upon request.

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Authors' contribution

ASA conceived the study. ZY, ASA and SS contributed in defining the search strategy. SB wrote the first draft of the manuscript. ZY, SS, SHR, SMT, TZ, MK, and SF facilitated with preparation of the manuscript and its finalization. All authors approved the final version of the manuscript.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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