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Exercise and Adiposity in Overweight and Obese Children and Adolescents: Protocol for a Systematic Review and Network Meta-Analysis of Randomised Trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019512
Article Type:	Protocol
Date Submitted by the Author:	07-Sep-2017
Complete List of Authors:	Kelley, George; West Virginia University, Biostatistics Kelley, Kristi; West Virginia University, Biostatistics Pate, Russell; University of South Carolina, Exercise Science
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Sports and exercise medicine, Public health, Paediatrics, Epidemiology
Keywords:	exercise, overweight, obesity, children, adolescents, network meta-analysis

Title: Exercise and Adiposity in Overweight and Obese Children and Adolescents: Protocol for a Systematic Review and Network Meta-Analysis of Randomised Trials

Authors: Corresponding author: *George A. Kelley*, DA, FACSM, School of Public Health, Department of Biostatistics, West Virginia University, Morgantown, WV, USA, 26506-9190, Office Phone: 304-293-6279, Fax: 304-293-5891, E-mail: gkelley@hsc.wvu.edu

Co-author: *Kristi S. Kelley*, M.Ed., Research Instructor, School of Public Health, Department of Biostatistics, Robert C. Byrd Health Sciences Center West Virginia University, PO Box 9190, Morgantown, WV, USA, 26506-9190, Office Phone: 304-293-6280, Fax: 304-293-5891, E-mail: kskelley@hsc.wvu.edu

Co-author: *Russell R. Pate*, PhD., FACSM, Director, Children's Physical Activity Research Group, Department of Exercise Science, University of South Carolina, Columbia, South Carolina, Office Phone: 803-777-2456, Fax: 803-777-2504, E-mail: rpate@mailbox.sc.edu

Keywords: exercise, overweight, obesity, children, adolescents, network meta-analysis

Word count: 4,142

ABSTRACT

Introduction: Overweight and obesity is a worldwide public health problem among children and adolescents. However, the magnitude of effect, as well as hierarchy of exercise interventions (aerobic, strength training, or both), on selected measures of adiposity is not well established despite numerous trials on this issue. The primary purposes of this study are to use the network meta-analytic approach to determine the effects and hierarchy of exercise interventions on selected measures of adiposity in overweight and obese children and adolescents. **Methods and analysis:** Randomised exercise intervention trials ≥ 4 weeks, published in any language between January 1, 1973 and August 31, 2017, and which include direct and/or indirect evidence, will be included. Studies will be located by searching five electronic databases, cross-referencing and expert review. Dual selection and abstraction of data will occur. The primary outcomes will be changes in body mass index (BMI in $kg{\cdot}m^2$), fat mass and percent body fat. Risk of bias will be assessed using the Cochrane Risk of Bias assessment instrument while confidence in the cumulative evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) instrument for network meta-analysis. Network meta-analysis will be performed using multivariate random-effects meta-regression models. The surface under the cumulative ranking curve (SUCRA) will be used to provide a hierarchy of exercise treatments (aerobic, strength, or both). **Dissemination:** The findings of this network meta-analysis will be presented at a professional conference and published in a peer-reviewed journal. **Trial registration number:** PROSPERO #CRD42017073103

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To the best of the investigative team's knowledge, this is the first systematic review to use the network meta-analytic approach to determine the effects as well as hierarchy of exercise interventions (aerobic, strength training, or both) on BMI in $kg \cdot m^2$, fat mass and percent body fat in overweight and obese children and adolescents.
- The results of this systematic review with network meta-analysis should be useful to practitioners and policy-makers for making informed decisions about exercise in the treatment of overweight and obesity in children and adolescents.
- The results of this systematic review with network meta-analysis should be useful to researchers with respect to the conduct and reporting of future research on this topic.
- Common to most meta-analyses, the results may yield significant heterogeneity which cannot be explained.
- Like any aggregate data meta-analysis, the possibility of ecological fallacy exists.

INTRODUCTION

Rationale

Overweight and obesity in children and adolescents is a major public health problem worldwide. Between 1980 and 2013, the worldwide prevalence of overweight and obesity in children and adolescents increased by 6.9%, from 16.9% to 23.8%, in boys and by 6.4%, from 16.2% to 22.6%, in girls from developed countries.[1] For developing countries, increases of 4.8%, from 8.1% to 12.9% for boys and 5%, from 8.4% to 13.4% in girls, were reported.[1] In the United States, the prevalence of overweight and obesity, defined as a body mass index (BMI) $\geq$ 85th percentile based on Centers for Disease Control Growth Charts, has been reported to be 31.8% among children and adolescents 2 to 19 years of age, while the prevalence of obesity, defined as a BMI $\geq$ 95th percentile, has been reported as 16.9%.[2] When compared to 30 years ago, this represents an obesity prevalence that is more than two times higher in US children and more than four times higher in adolescents.[2 3]

The economic costs associated with overweight and obesity among children and adolescents are also substantial. For example, Finkelstein et al. estimated that the incremental lifetime medical cost of an obese 10-year-old child in the US, relative to a normal weight child who maintained normal weight throughout adulthood, was $19,000.[4] Based on the number of obese 10-year-olds in the US, the total direct medical costs associated with obesity were estimated at $14 billion for this age only.[4]

The negative outcomes associated with obesity in children and adolescents are both immediate and long-term.[5] For immediacy, a population-based study of US children and adolescents 5 to 17 years of age found that approximately 70% of obese youth had a minimum of one cardiovascular disease risk factor (high cholesterol, high blood pressure, etc.).[6] Obese children and adolescents are also more likely to be diagnosed with prediabetes,[7] as well as being at an increased risk for bone and joint difficulties, sleep apnea, and social and psychological issues such as stigmatization, poor self-esteem, and poorer health-related quality-of-life.[8,9]

Long-term, childhood and adolescent overweight and obesity has been demonstrated to track into adulthood,[10-14] thus placing overweight and/or obese adults at a greater risk for cardiovascular disease, type 2 diabetes, stroke, several types of cancer, and osteoarthritis.[5] These long-term outcomes are important given that overweight and obesity has been reported to be the third leading cause of preventable death in the US, responsible for 216,000 deaths in 2005.[15] In addition, more recent research has shown that up to 18 percent of US deaths between 1986 and 2006 were attributed to obesity.[16] Furthermore, this issue has become so problematic that it is now recognized by the American Medical Association as a disease.[17] Not surprisingly, reducing the prevalence of overweight and obesity among children and adolescents is a major public health priority in the US.[18]

One promising intervention in the treatment of overweight and obesity is exercise. However, previous randomised trials that were limited to or included overweight and obese children and adolescents have led to conflicting results,[19-65] with some reporting statistically significant reductions in adiposity (BMI) as a primary outcome[19,20,23,24,29,34,35,38,48,58-63,66-70] and others reporting no change.[21,22,25-28,30-33,36,37,39-47,49-57,64,65,69,71,72] When limited to overweight and obese male and female children and adolescents,[19,21,24-27,29-33,35,38,40,43,45-48,52-64,50,51,52,54,55,56,57] only 18 (45.0%) have reported statistically significant reductions in BMI.[19 24 29 35 38 48 58,59-63 65, 50, 52, 54, 56, 57] While this may lead one to the general conclusion that exercise does little to reduce BMI in overweight and obese children and adolescents, this would be shortsighted since it relies on the vote-counting approach,[73] an approach that has been shown to be less valid than the meta-analytic approach.[73 74]

Previous systematic reviews with meta-analyses that have focused on the effects of exercise as an independent intervention on BMI as a primary outcome in male and female children and adolescents have reported conflicting findings with five reporting a significant improvement in BMI[75-79] and five others reporting no statistically significant improvement.[80-84] However, nine of the ten suffer from one or more of the following limitations: (1) inclusion of a small number of studies with exercise as the only intervention,[78 80-82] (2) inclusion of non-randomised trials,[75 81] (3) inclusion of children and adolescents who were not overweight or obese.[77 79 81 83 84] Relevant to this application, all ten suffer from both reliance on pairwise versus network meta-analysis, the latter of which incorporates both direct and indirect evidence. In addition, there was an absence of an established hierarchy for determining which types of exercise (aerobic, strength training, or both) might be best for improving BMI based on both direct and indirect evidence.[75-84] To partially address this issue as well as demonstrate feasibility, the investigative team has recently used the network meta-analytic approach to examine the effects of exercise (aerobic, strength training, or both) on BMI z-score in overweight and obese children and adolescents.[85 86] Statistically significant reductions in BMI z-score were found for aerobic exercise and combined aerobic and strength exercise, but not strength training alone (mean, 95% CI: aerobic, -0.10, -0.15 to -0.05;

aerobic and strength, -0.11, -0.19 to -0.03; strength, 0.04, -0.07 to 0.15).[86] Combined aerobic and strength training was ranked best, followed by aerobic exercise and then strength training.[86] Consistency in evidence and risk of bias did not differ between direct and indirect studies.[86] It was concluded that combined aerobic exercise and strength training as well as aerobic exercise alone are associated with reductions in BMI z-score.[86] The lack of effect on BMI z-score in the strength training studies may have been the result of increases in lean muscle mass. However, since BMI in $kg{\cdot}m^2$ continues to be the most frequently assessed and reported measure of adiposity in both the clinical and public health setting, an examination of such using the network meta-analytic approach is needed. In addition, since all types of BMI measures as well as body weight do not capture changes in body composition (fat mass, percent body fat, etc.), the inclusion of such outcomes, as previously suggested,[86] is also necessary.

Objectives

The primary objectives of the current study are to conduct a systematic review with network meta-analysis of randomised trials to (1) determine the effects of exercise (aerobic, strength training, or both) on adiposity (BMI in $kg{\cdot}m^2$, fat mass, percent body fat) in overweight and obese children and adolescents, and (2) establish a hierarchy of exercise interventions (aerobic, strength training, or both) for treating adiposity (BMI in $kg{\cdot}m^2$, fat mass, percent body fat) in overweight and obese children and adolescents.

METHODS

Overview

This study will follow the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension statement for network meta-analyses of health care interventions.[87] The protocol for this network meta-analysis is registered in PROSPERO (trial registration number CRD42017073103.

Eligibility criteria

The inclusion criteria for this proposed network meta-analysis will be as follows: (1) direct evidence from randomised trials that compare two or more exercise interventions (aerobic, strength training, both) or indirect evidence from randomised controlled trials that compare an exercise intervention group to a comparative control group (non-intervention, attention control, usual care, wait-list control, placebo), (2) exercise-only intervention (aerobic, strength training, or both), (3) studies lasting ≥ 4 weeks, (4) male and/or female children and adolescents 2 to 18 years of age, (5) participants overweight or obese, as defined by the authors, (6) studies published in any language that include an English language abstract, (7) studies published between January 1, 1973 and August 31, 2017, and (8) data available for BMI in $kg{\cdot}m^2$, fat mass or percent body fat.

Studies will be limited to randomised trials because it is the only way to control for confounders that are not known or measured as well as the observation that nonrandomised controlled trials tend to overestimate the effects of healthcare interventions.[88 89] Indirect evidence studies will be limited to randomised controlled trials with at least one exercise arm that participates in either aerobic, strength training, or a combination of aerobic and strength training exercise. Direct evidence studies will be limited to randomised trials that include at least two of the following exercise arms: (1) aerobic, (2) strength training, (3) aerobic and strength training exercise.

For the purposes of this study, exercise, aerobic exercise and strength training will be defined according to the 2008 Physical Activity Guidelines for Americans,[90] defined as movement that is "planned, structured, and repetitive and purposive in the sense that the improvement or maintenance of one or more components of physical fitness is the objective,"[90 91] aerobic exercise as "exercise that primarily uses the aerobic energy-producing systems, can improve the capacity and efficiency of these systems, and is effective for improving cardiorespiratory endurance,"[90] and strength training as "exercise training primarily designed to increase skeletal muscle strength, power, endurance, and mass".[90] Four weeks was chosen as the lower cut point for intervention length based on previous research demonstrating improvements in adiposity over this period of time in 11-year olds.[28]

Participants will be limited to overweight and obese children and adolescents, as defined by the original study authors, because it has been shown that this population is at an increased risk for premature morbidity and mortality throughout their lifetime.[92]

Studies will be limited to published articles and examined for potential small-study effects such as publication bias. Unpublished work, defined as master's theses, dissertations, abstracts from conference proceedings, technical reports, and studies conducted but never reported, will not be included. The rationale for this approach is based on the work of van Driel et al.[93] who concluded that (1) the difficulty in retrieving unpublished work could lead to selection bias, (2) many unpublished trials are eventually published, (3) the methodological quality of such studies are poorer than those that are published, and (4) the effort and resources required to obtain unpublished work may not be warranted.[93]

While some research has suggested that studies yielding statistically significant and positive results are more likely to be published in English-language versus non-English language journals,[94] other research has shown this to not be the case.[95] Given the former, studies from both English and non-English-language articles will be included with the latter translated into English by the second author using the freely available web-based Babelfish and Bing translators. For those studies that cannot be translated using Babelfish and/or Bing, professional translation services will be utilized.

The year 1973 was chosen as the starting point for searching based on a preliminary PubMed search that yielded the first study that met the search, but not necessarily eligibility, criteria.[96] Body mass index in $kg \cdot m^2$ was included as one of the three primary adiposity outcomes because it is the most commonly used and understood variable by practitioners as well as others and can be easily measured from body weight and height. However, because BMI is an indirect measure of adiposity, fat mass and percent body fat will be included because they are more direct measures of adiposity. The inclusion of fat mass and percent body fat may be especially relevant for studies that include strength training given that decreases in adiposity as measured by BMI may be offset by increases in muscle mass, a secondary outcome that will be coded.

Information sources

The following five electronic databases will be searched: (1) PubMed, (2) Web of Science, (3) Cochrane Central Register of Controlled Trials (CENTRAL), (4) Cumulative Index to Nursing and Allied Health Literature (CINAHL), and (5) Sport Discus. In addition to electronic database searches, cross-referencing will be conducted by examining the reference lists of previous review articles as well as each included study for potential articles that meet the inclusion criteria. Upon completion of initial searches, the third author will examine the reference list for thoroughness and completeness. Suggested studies will then be retrieved to see if they meet all inclusion criteria.

Search strategy

Search strategies specific to each database will be developed by the investigative team. Major keywords, or forms of keywords to include will be “random”, “children”, “adolescents”, “overweight”, “obese”, “exercise,” “physical fitness”, “body composition”, “fat mass”, “body fat”, “body composition”, “body mass index”, “adiposity”. Searches will be limited to studies published and indexed between January 1, 1973 and August 31, 2017, approximately 34 years. A copy of a preliminary search strategy using PubMed, including limits, can be found in Supplementary file 1. This search strategy will be adapted for other database searches. All database searches and article retrieval will be conducted by the second author with oversight from the first author.

Study records

Study selection

All studies to be screened will be imported into EndNote (version X8; New York, NY: Thomson-Reuters; 2016) and duplicates removed electronically and then manually by the second author. A copy of the database will then be provided to the first author for duplicate screening. To minimize selection bias, the first and second authors will select all studies, independent of each other. They will then review their selections for accuracy and consistency. The full report for each article will be retrieved for all titles and abstracts that appear to meet the inclusion criteria as well as those where uncertainty exists. Multiple reports for the same study will be addressed by including the most recently published article and drawing from prior reports, assuming the same methods and sample sizes are reported. Based on previous research suggesting neither a clinically nor statistically significant effect on results, blinding to journal titles, study authors, or institutions of the authors will not be employed during the screening and data abstraction processes.[97] Reasons for excluded studies will be recorded using the following categories: (1) inappropriate population, (2) inappropriate intervention, (3) inappropriate comparison(s), (4) inappropriate outcome(s), (5) inappropriate study design, (6) other. Upon the conclusion of screening, the first and second authors will meet and review their selections. Cohen's kappa statistic (κ) will be used to measure inter-selection agreement.[98] Any discrepancies will be resolved by consensus. If consensus cannot be reached, the third author will serve as an arbitrator. Upon selecting the final number of studies to include, the overall precision of the searches will be computed by dividing the number of included studies by the total number of studies screened after removing duplicates.[99] The number needed-to-read (NNR) will then be calculated as the reciprocal of the precision.[99] A flow diagram that describes the search procedure will be included as well as a supplementary file that includes a reference list of all excluded studies, including the reason(s) for exclusion. Figure 1 illustrates the proposed structure for the flow diagram.

Data abstraction

For this project, Microsoft Excel (version 2016; Redmond, WA: Microsoft Corporation; 2016) will be used to develop comprehensive electronic codebooks that will define the coding process for each of the variables coded. The codebook will be created by the first two authors with feedback from the third author. Consequently, the abstraction of data from the studies in this proposed project should require little subjective judgment on the part of the coder. The major groups of variables to code will include (1) study characteristics (author, journal, year of publication, etc.), (2) participant characteristics (age, gender, height, body weight, etc.), and (3) data for primary and secondary outcomes (sample sizes, baseline and post-exercise means and standard deviations, etc.). Table 1 contains a preliminary list of variables that will be coded. Based on previous research by the investigative team,[86] a codebook capable of including at least 242 items from each study is expected. To avoid data abstraction bias, the first two authors will independently code (dual-coding) all studies to ensure accuracy and consistency. Inter-rater agreement will be assessed using Cohen's kappa statistic (κ).[98] Any disagreement in the items coded will be discussed until mutual agreement is reached. If agreement cannot be reached, the third author will serve as an arbitrator.

Outcomes and prioritization

The primary outcomes in this study will be changes BMI in $kg{\cdot}m^2$, fat mass, and percent body fat in overweight and obese children and adolescents. Secondary outcomes will include body weight, lean body mass, waist circumference, waist-to-hip ratio, energy intake, energy expenditure, physical activity level, maximum oxygen consumption (relative and absolute), muscular strength, resting systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, ratio of total cholesterol to high-density lipoprotein cholesterol, non-high density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glycosylated hemoglobin, fasting and non-fasting glucose and insulin.

Risk of bias assessment in individual studies

Risk of bias for included studies will be assessed using the Cochrane Risk of Bias

Instrument.[100] Assessment is based on judgments of low, high or unclear risk of bias across six defined domains: (1) sequence generation, (2) allocation sequence concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessors, (5) incomplete outcome data, and (6) selective outcome reporting. A seventh domain, whether participants were exercising regularly, as defined by the original study authors prior to taking part in the study, will also be assessed. This risk of bias approach has been recommended over the use of study quality rating scales given the lack of empirical evidence to support the latter.[89 101 102] Assessment for risk of bias will be limited to the primary outcomes of interest, i.e., changes in BMI in kg·m^2, fat mass, and percent body fat. All studies will be classified as high risk of bias with respect to the category "blinding of participants and personnel" given that it's virtually impossible to blind participants to group assignment in exercise intervention protocols. Based on previous research, no study will be excluded based on risk of bias results.[103]

Data Synthesis

Calculation of effect sizes

The primary outcomes for this study will be changes in BMI in kg·m^2, fat mass (kg), and percent body fat using the original metric. Changes for indirect comparisons will be calculated by subtracting the change outcome difference in the exercise group minus the change outcome difference in the control group. Variances will be computed using the pooled standard deviations of change scores in the exercise and control groups. If change score standard deviations are not available, they will be calculated from 95% confidence intervals (CI) for either change outcome or treatment effect differences as well as pre and post standard deviation values, the latter according to procedures developed by Follmann et al.[104] For direct comparisons, i.e., randomised trials with no control group, the same general procedures will be followed except that the control group data will be replaced with one of the exercise interventions as follows: (1) aerobic minus strength training, (2) aerobic and strength training combined minus aerobic training, (3) aerobic and strength training combined minus strength training. Ninety-five percent CI and *z*-alpha values will be calculated for each outcome from each study. For those studies that include both direct and indirect comparisons, only direct comparison data will be included since a primary purpose of the current meta-analysis is determining which exercise interventions(s) might work best for improving adiposity in children and adolescents. For studies in which adiposity outcomes are assessed at multiple intervention time points, for example, 0, 8, and 16 weeks, only data from the initial and last assessment will be used. If follow-up data are available, results from such will also be analyzed separately to determine the sustainability of changes in adiposity. If any crossover trials are included, treatment effects will be calculated by using all assessments from the intervention and control periods and analyzing them similar to a parallel group trial.[105] While the possibility of a unit-of-analysis error exists as well as studies being under versus over-weighted, this method is believed to be better than alternative approaches, for example, limiting data from the first assessment point or trying to impute standard deviations, especially given the primary and secondary outcomes included and expected distribution of findings,.[105]

Secondary outcomes (body weight, lean body mass, waist circumference, waist-to-hip ratio, energy intake, energy expenditure, maximum oxygen consumption (relative and absolute), resting systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, ratio of total cholesterol to high-density lipoprotein cholesterol, non-high density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glycosylated hemoglobin, fasting and non-fasting glucose and insulin) will be handled using the same approach as for primary outcomes. However, given the different metrics expected and the inability to convert between them, changes in physical activity levels and muscular strength will be calculated using the standardized effect size, adjusted for small sample sizes.[106]

Pooled estimates for changes in outcomes

Network (geometry) plots for each outcome will be used to provide a visual representation of the evidence base with nodes (circles) weighted by the number of participants randomised to each treatment and edges (lines) weighted by the number of studies evaluating each pair of treatments.[107 108] *Contribution plots* for each outcome will be used to determine the most dominant comparisons for each network estimate as well as for the entire network.[107] The weights applied will be a function of the variance of the direct treatment effect and the network structure, the result being a percent contribution of each direct comparison to each network estimate.[107]

Network meta-analysis will be performed using *multivariate random-effects meta-regression models* that can be performed within a frequentist setting, allows for the inclusion of potential covariates, and correctly accounts for the correlations from multi-arm trials.[109 110] A two-tailed alpha value $\leq$ 0.05 and non-overlapping 95% CI will be considered to represent statistically significant changes. Separate network meta-analysis models will be used to examine for changes in each primary and secondary outcome. Potential *covariates* will be examined by (1) conducting simple meta-

356 regression for statistically significant associations between covariates and changes in primary outcomes (BMI in kg·m^2 , fat mass, percent fat), (2) examining for multicollinearity between covariates (r > 0.80), and (3) building a multiple meta-regression model. A list of potential covariates to examine using simple meta-regression is shown in Table 1. *Transitivity, i.e.,* similarity in the distribution of potential effect modifiers across the different pairwise comparisons for each outcome[111] will include those listed in Table 1. *Inconsistency*, i.e., differences in effect estimates between direct and indirect results for the same comparison,[112] will be checked by assessing differences in treatment effects between direct and indirect effect estimates as well as differences between trials with different designs, for example, two-arm versus multi-arm trials.[110 112 113] However, the probability of inconsistency is considered small given recent research demonstrating that inconsistency was detected in only 2% to 14% of tested loops, depending on the effect measure and heterogeneity estimation method.[114 115] Finally, *prediction intervals* will be used to enhance interpretation of results with respect to the magnitude of heterogeneity as well as provide an estimate of expected results in a future study.[116-118] For network meta-analysis, degrees of freedom (*df)* will be set to the number of studies – the number of comparisons – 1.[118]

Meta-biases

Small-study-effects (publication bias, etc.) will be assessed using comparison adjusted funnel plots.[107] In the absence of small-study effects, the comparison adjusted funnel plot should be symmetric around the zero line.

Confidence in cumulative evidence

378 *Quality analysis* of specific pairwise effect estimates in the network meta-analysis will
379 be evaluated using a recently developed modification of the Grading of
380 Recommendations Assessment, Development and Evaluation (GRADE) for network
381 meta-analysis across five domains: (1) study limitations, (2) indirectness, (3)
382 inconsistency, (4) imprecision, and (5) small-study effects.[119] Assessment will be
383 conducted using the same procedures as for study selection and data abstraction.

384 To establish a hierarchy of exercise interventions for selected outcomes in the current
385 meta-analysis, *ranking analysis,* i.e., the ability to rank all interventions for a single
386 outcome under study, for example changes in BMI in $kg{\cdot}m^2$, will be used based on
387 probabilities. However, because the ranking of treatments based exclusively on the
388 probability of each treatment being the best should be avoided given that it does not
389 account for the uncertainty in the relative treatment effects and the possibility for
390 assigning higher ranks for treatments in which little evidence is available, separate
391 *rankograms and cumulative ranking probability plots* will be used to present ranking
392 probabilities along with their uncertainty for changes in primary and secondary
393 outcomes.[107 120] The surface under the cumulative ranking curve (SUCRA), a
394 transformation of the mean rank, will be used to establish a hierarchy of exercise
395 interventions (aerobic, strength, both) while accounting for the location and variance of
396 all treatment effects.[107 120] Larger SUCRA values indicate better ranks for the
397 treatment.[107 120] Interpretation of all rankings will be approached from the perspective of
398 absolute and relative treatment effects.[108]

399 Software used for statistical analysis

All data will be analysed using Stata (V.14.1; Stata/SE for Windows, version 14.0. College Station, TX: Stata Corporation LP; 2015), Microsoft Excel (version 2016; Redmond, WA: Microsoft Corporation; 2016), and two add-ins for Excel, SSC-Stat (V.2.18; SSC-Stat, version 3.0. University of Reading, United Kingdom: Statistical Services Center; 2007), and EZ-Analyze (V.3.0; EZ Analyze, version 3.0. TA Poynton; 2007).

DISSEMINATION

The results of this study will be presented at a professional conference and published in a peer-reviewed journal.

CONTRIBUTORS

GAK is the guarantor. GAK, KSK and RRP drafted the manuscript. All authors contributed to (1) the development of the data sources to search for relevant literature, including search strategy, (2) selection criteria, (3) data extraction criteria and (4) risk of bias assessment strategy. GAK provided statistical expertise while RRP provided content expertise on exercise and adiposity in overweight and obese children and adolescents. All authors read, provided feedback, and approved the final manuscript.

REGISTRATION

In accordance with the Primary Reporting Items for Systematics Reviews and Meta-Analyses Protocols (PRISMA-P) statement, this systematic review with network meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on August 23, 2017 (#CRD42017073103).

AMENDMENTS TO PROTOCOL

None to date. If this protocol is amended, the date of each amendment, a description of the change, as well as a rationale for the change, will be provided.

COMPETING INTERESTS

None.

FUNDING

This study is funded by the American Heart Association, Grant #17GRNT33630158 (GA Kelley, Principal Investigator). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the American Heart Association.

DATA SHARING STATEMENT

All data will be available upon request from the corresponding author.

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Table 1. Covariates to examine using simple meta-regression.

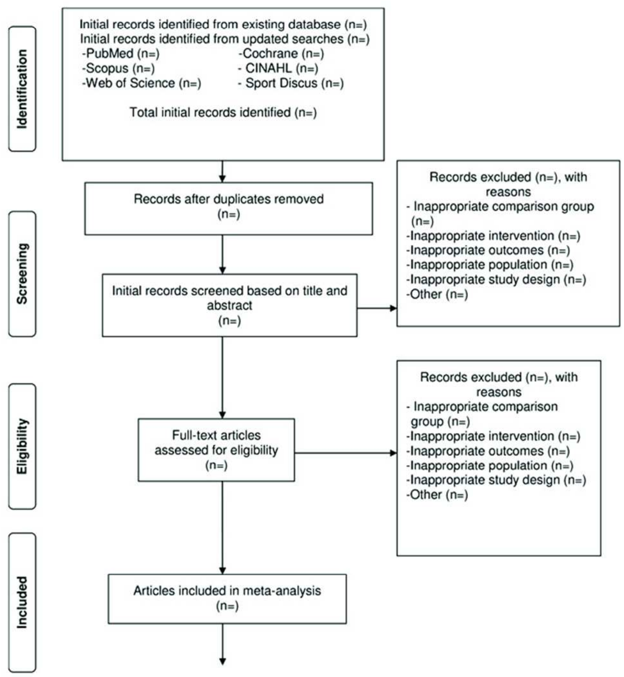
Characteristics	Variable
Study	Publication year, impact factor of journal, country study conducted, type of control group, bias (sequence generation, allocation concealment, blinding of participants & personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting), type of analysis
Participant	Age, gender, race/ethnicity, maturational stage
Exercise	Type (aerobic, strength, both), length, frequency, intensity, duration, total minutes, total minutes (adjusted for compliance), mode, compliance, exercise supervision, setting, number of sets, number of repetitions, rest between sets, number of exercises, type of resistance, equipment used, fidelity (design, training, delivery, receipt, enactment)
Outcome	Baseline values for primary outcomes (BMI in kg·m^{2}, fat mass, percent fat), method used to assess adiposity, i.e., instrumentation, body weight, lean body mass, waist circumference, waist-to-hip ratio, diet, energy intake, energy expenditure, physical activity level, non-exercise activity, maximum oxygen consumption (relative and absolute), muscular strength, resting systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, ratio of total cholesterol to high-density lipoprotein cholesterol, non-high density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glycosylated hemoglobin, fasting and non-fasting glucose and insulin

FIGURE LEGEND

Figure 1. Proposed flow diagram to depict the search process.

SUPPLEMENTARY FILE

Supplementary File 1. Preliminary search results in PubMed.



Flow diagram for network meta-analysis.

86x111mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Line #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	**1-2**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	**NA**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	**43; 150-151;416-420**
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	**4-7; 9-12;14-17**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	**409-415**
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	**421-423**
Support:			**426-430**
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	**58-138**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	**139-145**
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	**152-210**
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	**211-219**
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	**220-229; Supplementary file 1**
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	**232-234; 259-261;400-405**

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	**231-257; Figure 1**
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, duplicate), any processes for obtaining and confirming data from investigators	**258-274**
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources) any pre-planned data assumptions and simplifications	**264-270;275-284;Table 1**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	**275-284**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	**285-299**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	**300-372; 384-398; & Table 1 for 15a-d**
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	**373-376**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	**377-383**

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Exercise and Adiposity in Overweight and Obese Children and Adolescents: Protocol for a Systematic Review and Network Meta-Analysis of Randomised Trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019512.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Oct-2017
Complete List of Authors:	Kelley, George; West Virginia University, Biostatistics Kelley, Kristi; West Virginia University, Biostatistics Pate, Russell; University of South Carolina, Exercise Science
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Sports and exercise medicine, Public health, Paediatrics, Epidemiology
Keywords:	exercise, overweight, obesity, children, adolescents, network meta-analysis

Title: Exercise and Adiposity in Overweight and Obese Children and Adolescents: Protocol for a Systematic Review and Network Meta-Analysis of Randomised Trials

Authors: Corresponding author: *George A. Kelley*, DA, FACSM, School of Public Health, Department of Biostatistics, West Virginia University, Morgantown, WV, USA, 26506-9190, Office Phone: 304-293-6279, Fax: 304-293-5891, E-mail: gkelley@hsc.wvu.edu

Co-author: *Kristi S. Kelley*, M.Ed., Research Instructor, School of Public Health, Department of Biostatistics, Robert C. Byrd Health Sciences Center West Virginia University, PO Box 9190, Morgantown, WV, USA, 26506-9190, Office Phone: 304-293-6280, Fax: 304-293-5891, E-mail: kskelley@hsc.wvu.edu

Co-author: *Russell R. Pate*, PhD., FACSM, Director, Children's Physical Activity Research Group, Department of Exercise Science, University of South Carolina, Columbia, South Carolina, Office Phone: 803-777-2456, Fax: 803-777-2504, E-mail: rpate@mailbox.sc.edu

Keywords: exercise, overweight, obesity, children, adolescents, network meta-analysis

Word count: 3,822

ABSTRACT

Introduction: Overweight and obesity is a worldwide public health problem among children and adolescents. However, the magnitude of effect, as well as hierarchy of exercise interventions (aerobic, strength training, or both), on selected measures of adiposity is not well established despite numerous trials on this issue. The primary purposes of this study are to use the network meta-analytic approach to determine the effects and hierarchy of exercise interventions on selected measures of adiposity in overweight and obese children and adolescents. **Methods and analysis:** Randomised exercise intervention trials $\geq$ 4 weeks, available in any language up to August 31, 2017 and which include direct and/or indirect evidence, will be included. Studies will be located by searching seven electronic databases, cross-referencing and expert review. Dual selection and abstraction of data will occur. The primary outcomes will be changes in body mass index (BMI in kg/m^2), fat mass and percent body fat. Risk of bias will be assessed using the Cochrane Risk of Bias assessment instrument while confidence in the cumulative evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) instrument for network meta-analysis. Network meta-analysis will be performed using multivariate random-effects meta-regression models. The surface under the cumulative ranking curve (SUCRA) will be used to provide a hierarchy of exercise treatments (aerobic, strength, or both). **Dissemination:** The findings of this network meta-analysis will be presented at a professional conference and published in a peer-reviewed journal. **Trial registration number:** PROSPERO #CRD42017073103

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To the best of the investigative team's knowledge, this is the first systematic review to use the network meta-analytic approach to determine the effects as well as hierarchy of exercise interventions (aerobic, strength training, or both) on BMI in kg/m^2, fat mass and percent body fat in overweight and obese children and adolescents.

- The results of this systematic review with network meta-analysis should be useful to practitioners and policy-makers for making informed decisions about exercise in the treatment of overweight and obesity in children and adolescents.

- The results of this systematic review with network meta-analysis should be useful to researchers with respect to the conduct and reporting of future research on this topic.

- Common to most meta-analyses, the results may yield significant heterogeneity which cannot be explained.

- Like any aggregate data meta-analysis, the possibility of ecological fallacy exists, i.e., that group averages are not reflective of an individual's values.

INTRODUCTION

Rationale

Overweight and obesity in children and adolescents is a major public health problem worldwide. Between 1980 and 2013, the worldwide prevalence of overweight and obesity in children and adolescents increased by 6.9%, from 16.9% to 23.8%, in boys and by 6.4%, from 16.2% to 22.6%, in girls from developed countries.[1] For developing countries, increases of 4.8%, from 8.1% to 12.9% for boys and 5%, from 8.4% to 13.4% in girls, were reported.[1]

The negative outcomes associated with obesity in children and adolescents are both immediate and long-term.[2] For immediacy, a population-based study of children and adolescents 5 to 17 years of age found that approximately 70% of obese youth had a minimum of one cardiovascular disease risk factor (high cholesterol, high blood pressure, etc.).[3] Obese children and adolescents are also more likely to be diagnosed with prediabetes,[4] as well as being at an increased risk for bone and joint difficulties, sleep apnea, and social and psychological issues such as stigmatization, poor self-esteem, and poorer health-related quality-of-life.[5 6] Long-term, childhood and adolescent overweight and obesity has been demonstrated to track into adulthood,[7-11] thus placing overweight and/or obese adults at a greater risk for cardiovascular disease, type 2 diabetes, stroke, several types of cancer, and osteoarthritis.[2]

One promising intervention in the treatment of overweight and obesity is exercise. However, previous randomised trials that were limited to or included overweight and obese children and adolescents have led to conflicting results,[12-58] with some reporting statistically significant reductions in adiposity (BMI) as a primary outcome[12 13 16 17 22 27 28]

[31 41 51-56 59-63] and others reporting no change.[14 15 18-21 23-26 29 30 32-40 42-50 57 58 62 64 65] When limited to overweight and obese male and female children and adolescents,[12 14 17-20 22-26 28 31 33 36 38-41 45-57 50, 51, 52, 54, 55, 56, 57] only 18 (45.0%) have reported statistically significant reductions in BMI.[12 17 22 28 31 41 51,52-56 58, 50, 52, 54, 56, 57] While this may lead one to the general conclusion that exercise does little to reduce BMI in overweight and obese children and adolescents, this would be shortsighted since it relies on the vote-counting approach,[66] an approach that has been shown to be less valid than the meta-analytic approach.[66 67]

Previous systematic reviews with meta-analyses that have focused on the effects of exercise as an independent intervention on BMI as a primary outcome in male and female children and adolescents have reported conflicting findings with five reporting a significant improvement in BMI[68-72] and five others reporting no statistically significant improvement.[73-77] However, nine of the ten suffer from one or more of the following limitations: (1) inclusion of a small number of studies with exercise as the only intervention,[71 73-75] (2) inclusion of non-randomised trials,[68 74] (3) inclusion of children and adolescents who were not overweight or obese.[70 72 74 76 77] Relevant to this application, all ten suffer from both reliance on pairwise versus network meta-analysis, the latter of which incorporates both direct and indirect evidence. In addition, there was an absence of an established hierarchy for determining which types of exercise (aerobic, strength training, or both) might be best for improving BMI based on both direct and indirect evidence.[68-77] To partially address this issue as well as demonstrate feasibility, the investigative team has recently used the network meta-analytic approach to examine the effects of exercise (aerobic, strength training, or both) on BMI z-score in overweight and obese children and adolescents.[78 79] Statistically significant reductions in BMI z-score were found for aerobic exercise and combined aerobic and strength exercise, but not strength training alone (mean, 95% CI: aerobic, -0.10, -0.15 to -0.05; aerobic and strength, -0.11, -0.19 to -0.03; strength, 0.04, -0.07 to 0.15).[79] Combined aerobic and strength training was ranked best, followed by aerobic exercise and then strength training.[79] Consistency in evidence and risk of bias did not differ between direct and indirect studies.[79] It was concluded that combined aerobic exercise and strength training as well as aerobic exercise alone are associated with reductions in BMI z-score.[79] The lack of effect on BMI z-score in the strength training studies may have been the result of increases in lean muscle mass. However, since BMI in kg/m^2 continues to be the most frequently assessed and reported measure of adiposity in both the clinical and public health setting, an examination of such using the network meta-analytic approach is needed. In addition, since all types of BMI measures as well as body weight do not capture changes in body composition (fat mass, percent body fat, etc.), the inclusion of such outcomes, as previously suggested,[79] is also necessary.

Objectives

The primary objectives of the current study are to conduct a systematic review with network meta-analysis of randomised trials to (1) determine the effects of exercise (aerobic, strength training, or both) on adiposity (BMI in kg/m^2, fat mass, percent body fat) in overweight and obese children and adolescents, and (2) establish a hierarchy of exercise interventions (aerobic, strength training, or both) for treating adiposity (BMI in kg/m^2, fat mass, percent body fat) in overweight and obese children and adolescents.

METHODS

Overview

This study will follow the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension statement for network meta-analyses of health care interventions.[80] The protocol for this network meta-analysis is registered in PROSPERO (trial registration number CRD42017073103.

Eligibility criteria

The inclusion criteria for this proposed network meta-analysis will be as follows: (1) direct evidence from randomised trials that compare two or more exercise interventions (aerobic, strength training, both) or indirect evidence from randomised controlled trials that compare an exercise intervention group to a comparative control group (non-intervention, attention control, usual care, wait-list control, placebo), (2) exercise-only intervention (aerobic, strength training, or both), (3) studies lasting ≥ 4 weeks, (4) male and/or female children and adolescents 2 to 18 years of age, (5) participants overweight or obese, as defined by the authors, (6) studies published in any language up to August 31, 2017, (7) data available for BMI in kg/m^2, fat mass or percent body fat.

Studies will be limited to randomised trials because it is the only way to control for confounders that are not known or measured as well as the observation that nonrandomised controlled trials tend to overestimate the effects of healthcare interventions.[81 82] Indirect evidence studies will be limited to randomised controlled trials with at least one exercise arm that participates in either aerobic, strength training, or a combination of aerobic and strength training exercise. Direct evidence studies will be limited to randomised trials that include at least two of the following exercise arms: (1) aerobic, (2) strength training, (3) aerobic and strength training exercise.

For the purposes of this study, exercise, aerobic exercise and strength training will be defined according to the 2008 Physical Activity Guidelines for Americans,[83] defined as movement that is “planned, structured, and repetitive and purposive in the sense that the improvement or maintenance of one or more components of physical fitness is the objective,”[83 84] aerobic exercise as “exercise that primarily uses the aerobic energy-producing systems, can improve the capacity and efficiency of these systems, and is effective for improving cardiorespiratory endurance,”[83] and strength training as “exercise training primarily designed to increase skeletal muscle strength, power, endurance, and mass”.[83] Four weeks was chosen as the lower cut point for intervention length based on previous research demonstrating improvements in adiposity over this period of time in 11-year olds.[21]

Participants will be limited to overweight and obese children and adolescents, as defined by the original study authors, because it has been shown that this population is at an increased risk for premature morbidity and mortality throughout their lifetime.[85]

While some research has suggested that studies yielding statistically significant and positive results are more likely to be published in English-language versus non-English language journals,[86] other research has shown this to not be the case.[87] Given the former, studies from both English and non-English-language articles will be included with the latter translated into English by the second author using the freely available web-based Babelfish and Bing translators. For those studies that cannot be translated using Babelfish and/or Bing, professional translation services will be utilized.

Body mass index in kg$\cdot$m^2 was included as one of the three primary adiposity outcomes because it is the most commonly used and understood variable by practitioners as well as others and can be easily measured from body weight and height. However, because BMI is an indirect measure of adiposity, fat mass and percent body fat will be included because they are more direct measures of adiposity. The inclusion of fat mass and percent body fat may be especially relevant for studies that include strength training given that decreases in adiposity as measured by BMI may be offset by increases in muscle mass, a secondary outcome that will be coded.

Information sources

The following seven electronic databases will be searched: (1) PubMed, (2) Web of Science, (3) Cochrane Central Register of Controlled Trials (CENTRAL), (4) Cumulative Index to Nursing and Allied Health Literature (CINAHL), (5) Sport Discus, (6) Translating Research into Practice (TRIP) and (7) ProQuest Dissertations and Theses. In addition to electronic database searches, cross-referencing will be conducted by examining the reference lists of previous review articles as well as each included study for potential articles that meet the inclusion criteria. Upon completion of initial searches, the third author will examine the reference list for thoroughness and completeness. Suggested studies will then be retrieved to see if they meet all inclusion criteria.

Search strategy

Search strategies specific to each database will be developed by the investigative team. Major keywords, or forms of keywords to include will be “random”, “children”, “adolescents”, “overweight”, “obese”, “exercise,” “physical fitness”, “body composition”, “fat mass”, “body fat”, “body composition”, “body mass index”, “adiposity”. A copy of a preliminary search strategy using PubMed, including limits, can be found in Supplementary file 1. This search strategy will be adapted for other database searches.

All database searches and article retrieval will be conducted by the second author with oversight from the first author.

Study records

Study selection

All studies to be screened will be imported into EndNote (version X8; New York, NY: Thomson-Reuters; 2016) and duplicates removed electronically and then manually by the second author. A copy of the database will then be provided to the first author for duplicate screening. To minimize selection bias, the first and second authors will select all studies, independent of each other. They will then review their selections for accuracy and consistency. The full report for each article will be retrieved for all titles and abstracts that appear to meet the inclusion criteria as well as those where uncertainty exists. Multiple reports for the same study will be addressed by including the most recently published article and drawing from prior reports, assuming the same methods and sample sizes are reported. Based on previous research suggesting neither a clinically nor statistically significant effect on results, blinding to journal titles, study authors, or institutions of the authors will not be employed during the screening and data abstraction processes.[88] Reasons for excluded studies will be recorded using the following categories: (1) inappropriate population, (2) inappropriate intervention, (3) inappropriate comparison(s), (4) inappropriate outcome(s), (5) inappropriate study design, (6) other. Upon the conclusion of screening, the first and second authors will meet and review their selections. Cohen's kappa statistic (κ) will be used to measure inter-selection agreement.[89] Any discrepancies will be resolved by consensus. If consensus cannot be reached, the third author will serve as an arbitrator. Upon selecting the final number of studies to include, the overall precision of the searches will be computed by dividing the number of included studies by the total number of studies screened after removing duplicates.[90] The number needed-to-read (NNR) will then be calculated as the reciprocal of the precision.[90] A flow diagram that describes the search procedure will be included as well as a supplementary file that includes a reference list of all excluded studies, including the reason(s) for exclusion. Figure 1 illustrates the proposed structure for the flow diagram.

Data abstraction

For this project, Microsoft Excel (version 2016; Redmond, WA: Microsoft Corporation; 2016) will be used to develop comprehensive electronic codebooks that will define the coding process for each of the variables coded. The codebook will be created by the first two authors with feedback from the third author. Consequently, the abstraction of data from the studies in this proposed project should require little subjective judgment on the part of the coder. The major groups of variables to code will include (1) study characteristics (author, journal, year of publication, etc.), (2) participant characteristics (age, gender, height, body weight, etc.), and (3) data for primary and secondary outcomes (sample sizes, baseline and post-exercise means and standard deviations, etc.). Table 1 contains a preliminary list of variables that will be coded. Based on previous research by the investigative team,[79] a codebook capable of including at least 242 items from each study is expected. To avoid data abstraction bias, the first two authors will independently code (dual-coding) all studies to ensure accuracy and consistency. Inter-rater agreement will be assessed using Cohen's kappa statistic (κ).[89] Any disagreement in the items coded will be discussed until mutual agreement is reached. If agreement cannot be reached, the third author will serve as an arbitrator.

Outcomes and prioritization

The primary outcomes in this study will be changes BMI in $kg^{/}m^{2}$, fat mass, and percent body fat in overweight and obese children and adolescents. Secondary outcomes will include body weight, lean body mass, waist circumference, waist-to-hip ratio, energy intake, energy expenditure, physical activity level, maximum oxygen consumption (relative and absolute), muscular strength, resting systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, ratio of total cholesterol to high-density lipoprotein cholesterol, non-high density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glycosylated hemoglobin, fasting and non-fasting glucose and insulin.

Risk of bias assessment in individual studies

Risk of bias for included studies will be assessed using the Cochrane Risk of Bias Instrument.[91] Assessment is based on judgments of low, high or unclear risk of bias across six defined domains: (1) sequence generation, (2) allocation sequence concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessors, (5) incomplete outcome data, and (6) selective outcome reporting. A seventh domain, whether participants were exercising regularly, as defined by the original study authors prior to taking part in the study, will also be assessed using the same approach as for the other six domains. As previously recommended, study-level results will reported for each domain according to risk of bias (low, high, or unclear) while the percentage of low, high, or unclear results across each domain will also be reported.[91] This risk of bias approach has been recommended over the use of study quality rating scales given the lack of empirical evidence to support the latter.[82 92 93] Assessment for risk of bias will be limited to the primary outcomes of interest, i.e., changes in BMI in kg/m^2, fat mass, and percent body fat. All studies will be classified as high risk of bias with respect to the category "blinding of participants and personnel" given that it's virtually impossible to blind participants to group assignment in exercise intervention protocols. Based on previous research, no study will be excluded based on risk of bias results.[94]

Data Synthesis

Calculation of effect sizes

The primary outcomes for this study will be changes in BMI in kg/m^2, fat mass (kg), and percent body fat using the original metric. Changes for indirect comparisons will be calculated by subtracting the change outcome difference in the exercise group minus the change outcome difference in the control group. Variances will be computed using the pooled standard deviations of change scores in the exercise and control groups. If change score standard deviations are not available, they will be calculated from 95% confidence intervals (CI) for either change outcome or treatment effect differences as well as pre and post standard deviation values, the latter according to procedures developed by Follmann et al.[95] For direct comparisons, i.e., randomised trials with no control group, the same general procedures will be followed except that the control group data will be replaced with one of the exercise interventions as follows: (1) aerobic minus strength training, (2) aerobic and strength training combined minus aerobic training, (3) aerobic and strength training combined minus strength training. Ninety-five percent CI and *z*-alpha values will be calculated for each outcome from each study. For those studies that include both direct and indirect comparisons, only direct comparison data will be included since a primary purpose of the current meta-analysis is determining which exercise interventions(s) might work best for improving adiposity in children and adolescents. For studies in which adiposity outcomes are assessed at multiple intervention time points, for example, 0, 8, and 16 weeks, only data from the initial and last assessment will be used. If follow-up data are available, results from such will also be analyzed separately to determine the sustainability of changes in adiposity. If any crossover trials are included, treatment effects will be calculated by using all assessments from the intervention and control periods and analyzing them similar to a parallel group trial.[96] While the possibility of a unit-of-analysis error exists as well as studies being under versus over-weighted, this method is believed to be better than alternative approaches, for example, limiting data from the first assessment point or trying to impute standard deviations, especially given the primary and secondary outcomes included and expected distribution of findings,.[96]

Secondary outcomes (body weight, lean body mass, waist circumference, waist-to-hip ratio, energy intake, energy expenditure, maximum oxygen consumption (relative and absolute), resting systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, ratio of total cholesterol to high-density lipoprotein cholesterol, non-high density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glycosylated hemoglobin, fasting and non-fasting glucose and insulin) will be handled using the same approach as for primary outcomes. However, given the different metrics expected and the inability to convert between them, changes in physical activity levels and muscular strength will be calculated using the standardized effect size, adjusted for small sample sizes.[97]

Pooled estimates for changes in outcomes

Network (geometry) plots for each outcome will be used to provide a visual representation of the evidence base with nodes (circles) weighted by the number of participants randomised to each treatment and edges (lines) weighted by the number of studies evaluating each pair of treatments.[98 99] *Contribution plots* for each outcome will be used to determine the most dominant comparisons for each network estimate as well as for the entire network.[98] The weights applied will be a function of the variance of the direct treatment effect and the network structure, the result being a percent contribution of each direct comparison to each network estimate.[98]

Network meta-analysis will be performed using *multivariate random-effects meta-regression models* that can be performed within a frequentist setting, allows for the inclusion of potential covariates, and correctly accounts for the correlations from multi-arm trials.[100 101] A two-tailed alpha value $\leq$ 0.05 and non-overlapping 95% CI will be considered to represent statistically significant changes. Separate network meta-analysis models will be used to examine for changes in each primary and secondary outcome. Potential *covariates* will be examined by (1) conducting simple meta-regression for statistically significant associations between covariates and changes in primary outcomes (BMI in kg/m^2 , fat mass, percent fat), (2) examining for multicollinearity between covariates (r > 0.80), and (3) building a multiple meta-regression model. A list of potential covariates to examine using simple meta-regression is shown in Table 1. While we will include all methods used to assess adiposity, we will also conduct sensitivity analyses to see if results differ according to method of assessment, for example, fat mass assessed using whole body magnetic resonance imaging versus bioelectrical impedance. Secondary outcomes (energy intake and expenditure, physical activity level, muscular strength) will be handled using the same approach. *Transitivity, i.e.,* similarity in the distribution of potential effect modifiers across the different pairwise comparisons for each outcome[102] will include those listed in Table 1. *Inconsistency*, i.e., differences in effect estimates between direct and indirect results for the same comparison,[103] will be checked by assessing differences in treatment effects between direct and indirect effect estimates as well as differences between trials with different designs, for example, two-arm versus multi-arm trials.[101 103 104] However, the probability of inconsistency is considered small given recent research demonstrating that inconsistency was detected in only 2% to 14% of tested loops, depending on the effect measure and heterogeneity estimation method.[105 106] Finally, *prediction intervals* will be used to enhance interpretation of results with respect to the magnitude of heterogeneity as well as provide an estimate of expected results in a future study.[107-109] For network meta-analysis, degrees of freedom (*df)* will be set to the number of studies – the number of comparisons – 1.[109]

Meta-biases

Small-study-effects (publication bias, etc.) will be assessed using comparison adjusted funnel plots.[98] In the absence of small-study effects, the comparison adjusted funnel plot should be symmetric around the zero line.

Confidence in cumulative evidence

Quality analysis of specific pairwise effect estimates in the network meta-analysis will be evaluated using a recently developed modification of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) for network meta-analysis across five domains: (1) study limitations, (2) indirectness, (3) inconsistency, (4) imprecision, and (5) small-study effects.[110] Assessment will be conducted using the same procedures as for study selection and data abstraction.

To establish a hierarchy of exercise interventions for selected outcomes in the current meta-analysis, *ranking analysis,* i.e., the ability to rank all interventions for a single outcome under study, for example changes in BMI in kg/m^2, will be used based on probabilities. However, because the ranking of treatments based exclusively on the probability of each treatment being the best should be avoided given that it does not account for the uncertainty in the relative treatment effects and the possibility for assigning higher ranks for treatments in which little evidence is available, separate *rankograms and cumulative ranking probability plots* will be used to present ranking probabilities along with their uncertainty for changes in primary and secondary outcomes.[98 111] The surface under the cumulative ranking curve (SUCRA), a transformation of the mean rank, will be used to establish a hierarchy of exercise interventions (aerobic, strength, both) while accounting for the location and variance of all treatment effects.[98 111] Larger SUCRA values indicate better ranks for the treatment.[98 111] Interpretation of all rankings will be approached from the perspective of absolute and relative treatment effects.[99]

Software used for statistical analysis

All data will be analysed using Stata (V.14.1; Stata/SE for Windows, version 14.0. College Station, TX: Stata Corporation LP; 2015), Microsoft Excel (version 2016; Redmond, WA: Microsoft Corporation; 2016), and two add-ins for Excel, SSC-Stat (V.2.18; SSC-Stat, version 3.0. University of Reading, United Kingdom: Statistical Services Center; 2007), and EZ-Analyze (V.3.0; EZ Analyze, version 3.0. TA Poynton; 2007).

DISSEMINATION

The results of this study will be presented at a professional conference and published in a peer-reviewed journal.

CONTRIBUTORS

GAK is the guarantor. GAK, KSK and RRP drafted the manuscript. All authors contributed to (1) the development of the data sources to search for relevant literature, including search strategy, (2) selection criteria, (3) data extraction criteria and (4) risk of bias assessment strategy. GAK provided statistical expertise while RRP provided content expertise on exercise and adiposity in overweight and obese children and adolescents. All authors read, provided feedback, and approved the final manuscript.

REGISTRATION

In accordance with the Primary Reporting Items for Systematics Reviews and Meta-Analyses Protocols (PRISMA-P) statement, this systematic review with network meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on August 23, 2017 (#CRD42017073103).

AMENDMENTS TO PROTOCOL

None to date. If this protocol is amended, the date of each amendment, a description of the change, as well as a rationale for the change, will be provided.

COMPETING INTERESTS

None.

FUNDING

This study is funded by the American Heart Association, Grant #17GRNT33630158 (GA Kelley, Principal Investigator). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the American Heart Association.

DATA SHARING STATEMENT

All data will be available upon request from the corresponding author.

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Table 1. Covariates to examine using simple meta-regression.

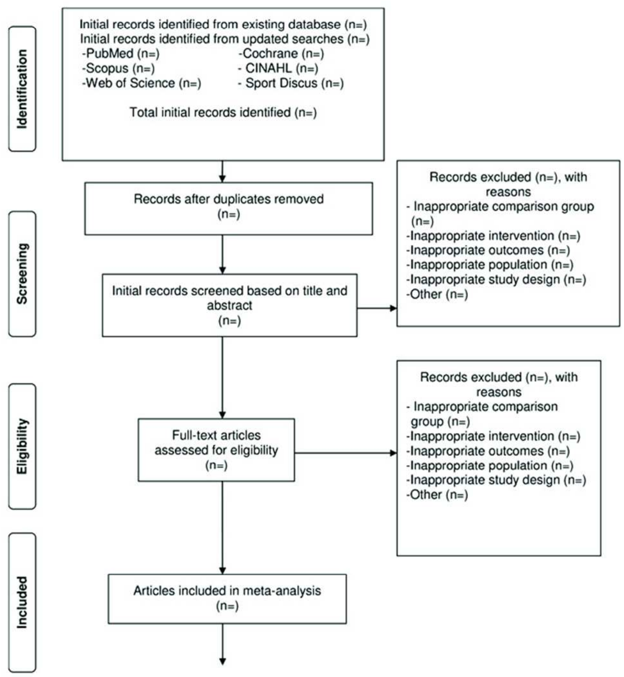
Characteristics	Variable
Study	Publication year, impact factor of journal, country study conducted, type of control group, bias (sequence generation, allocation concealment, blinding of participants & personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting), type of analysis
Participant	Age, gender, race/ethnicity, maturational stage
Exercise	Type (aerobic, strength, both), length, frequency, intensity, duration, total minutes, total minutes (adjusted for compliance), mode, compliance, exercise supervision, setting, number of sets, number of repetitions, rest between sets, number of exercises, type of resistance, equipment used, fidelity (design, training, delivery, receipt, enactment)
Outcome	Baseline values for primary outcomes (BMI in kg/m^2, fat mass, percent fat), method used to assess adiposity, i.e., instrumentation, body weight, lean body mass, waist circumference, waist-to-hip ratio, diet, energy intake, energy expenditure, physical activity level, non-exercise activity, maximum oxygen consumption (relative and absolute), muscular strength, resting systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, ratio of total cholesterol to high-density lipoprotein cholesterol, non-high density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glycosylated hemoglobin, fasting and non-fasting glucose and insulin

FIGURE LEGEND

Figure 1. Proposed flow diagram to depict the search process.

SUPPLEMENTARY FILE

Supplementary File 1. Preliminary search results in PubMed.



Flow diagram for network meta-analysis.

86x111mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Line #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	**1-2**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	**NA**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	**43; 131-132;394-398**
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	**4-7; 9-12;14-17**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	**387-393**
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	**399-401**
Support:			**404-408**
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	**60-119**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	**120-126**
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	**133-179**
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	**180-189**
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	**190-198; Supplementary file 1**
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	**201-202; 228-230;378-383**

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	**201-226; Figure 1**
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, duplicate), any processes for obtaining and confirming data from investigators	**227-243**
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources) any pre-planned data assumptions and simplifications	**233-239;244-253;Table 1**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	**244-253**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	**254-272**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	**274-350; 362-376; & Table 1 for 15a-d**
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	**351-354**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	**355-361**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Exercise and Adiposity in Overweight and Obese Children and Adolescents: Protocol for a Systematic Review and Network Meta-Analysis of Randomised Trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019512.R2
Article Type:	Protocol
Date Submitted by the Author:	17-Nov-2017
Complete List of Authors:	Kelley, George; West Virginia University, Biostatistics Kelley, Kristi; West Virginia University, Biostatistics Pate, Russell; University of South Carolina, Exercise Science
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Sports and exercise medicine, Public health, Paediatrics, Epidemiology
Keywords:	exercise, overweight, obesity, children, adolescents, network meta-analysis

Exercise and Adiposity in Overweight and Obese Children and Adolescents: Protocol for a Systematic Review and Network Meta-Analysis of Randomised Trials

Corresponding author: George A. Kelley, DA, FACSM, School of Public Health, Department of Biostatistics, West Virginia University, Morgantown, WV, USA, 26506-9190, Office Phone: 304-293-6279, Fax: 304-293-5891, E-mail: gkelley@hsc.wvu.edu

Co-author: Kristi S. Kelley, M.Ed., Research Instructor, School of Public Health, Department of Biostatistics, Robert C. Byrd Health Sciences Center West Virginia University, PO Box 9190, Morgantown, WV, USA, 26506-9190, Office Phone: 304-293-6280, Fax: 304-293-5891, E-mail: kskelley@hsc.wvu.edu

Co-author: Russell R. Pate, PhD., FACSM, Director, Children's Physical Activity Research Group, Department of Exercise Science, University of South Carolina, Columbia, South Carolina, Office Phone: 803-777-2456, Fax: 803-777-2504, E-mail: rpate@mailbox.sc.edu

Keywords: exercise, overweight, obesity, children, adolescents, network meta-analysis

Word count: 3,822

ABSTRACT

Introduction: Overweight and obesity is a worldwide public health problem among children and adolescents. However, the magnitude of effect, as well as hierarchy of exercise interventions (aerobic, strength training, or both), on selected measures of adiposity is not well established despite numerous trials on this issue. The primary purposes of this study are to use the network meta-analytic approach to determine the effects and hierarchy of exercise interventions on selected measures of adiposity in overweight and obese children and adolescents. **Methods and analysis:** Randomised exercise intervention trials $\geq$ 4 weeks, available in any language up to August 31, 2017 and which include direct and/or indirect evidence, will be included. Studies will be located by searching seven electronic databases, cross-referencing and expert review. Dual selection and abstraction of data will occur. The primary outcomes will be changes in body mass index (BMI in kg/m^2), fat mass and percent body fat. Risk of bias will be assessed using the Cochrane Risk of Bias assessment instrument while confidence in the cumulative evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) instrument for network meta-analysis. Network meta-analysis will be performed using multivariate random-effects meta-regression models. The surface under the cumulative ranking curve (SUCRA) will be used to provide a hierarchy of exercise treatments (aerobic, strength, or both). Ethics and **Dissemination:** This study does not require ethics approval. Findings will be presented at a professional conference and published in a peer-reviewed journal. **Trial registration number:** PROSPERO #CRD42017073103

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To the best of the investigative team's knowledge, this is the first systematic review to use the network meta-analytic approach to determine the effects as well as hierarchy of exercise interventions (aerobic, strength training, or both) on BMI in kg/m^2, fat mass and percent body fat in overweight and obese children and adolescents.

- The results of this systematic review with network meta-analysis should be useful to practitioners and policy-makers for making informed decisions about exercise in the treatment of overweight and obesity in children and adolescents.

- The results of this systematic review with network meta-analysis should be useful to researchers with respect to the conduct and reporting of future research on this topic.

- Common to most meta-analyses, the results may yield significant heterogeneity which cannot be explained.

- Like any aggregate data meta-analysis, the possibility of ecological fallacy exists, i.e., that group averages are not reflective of an individual's values.

INTRODUCTION

Rationale

Overweight and obesity in children and adolescents is a major public health problem worldwide. Between 1980 and 2013, the worldwide prevalence of overweight and obesity in children and adolescents increased by 6.9%, from 16.9% to 23.8%, in boys and by 6.4%, from 16.2% to 22.6%, in girls from developed countries.[1] For developing countries, increases of 4.8%, from 8.1% to 12.9% for boys and 5%, from 8.4% to 13.4% in girls, were reported.[1]

The negative outcomes associated with obesity in children and adolescents are both immediate and long-term.[2] For immediacy, a population-based study of children and adolescents 5 to 17 years of age found that approximately 70% of obese youth had a minimum of one cardiovascular disease risk factor (high cholesterol, high blood pressure, etc.).[3] Obese children and adolescents are also more likely to be diagnosed with prediabetes,[4] as well as being at an increased risk for bone and joint difficulties, sleep apnea, and social and psychological issues such as stigmatization, poor self-esteem, and poorer health-related quality-of-life.[5 6] Long-term, childhood and adolescent overweight and obesity has been demonstrated to track into adulthood,[7-11] thus placing overweight and/or obese adults at a greater risk for cardiovascular disease, type 2 diabetes, stroke, several types of cancer, and osteoarthritis.[2]

One promising intervention in the treatment of overweight and obesity is exercise. However, previous randomised trials that were limited to or included overweight and obese children and adolescents have led to conflicting results,[12-58] with some reporting statistically significant reductions in adiposity (BMI) as a primary outcome[12 13 16 17 22 27 28]

[31 41 51-56 59-63] and others reporting no change.[14 15 18-21 23-26 29 30 32-40 42-50 57 58 62 64 65] When limited to overweight and obese male and female children and adolescents,[12 14 17-20 22-26 28 31 33 36 38-41 45-57 50, 51, 52, 54, 55, 56, 57] only 18 (45.0%) have reported statistically significant reductions in BMI.[12 17 22 28 31 41 51,52-56 58, 50, 52, 54, 56, 57] While this may lead one to the general conclusion that exercise does little to reduce BMI in overweight and obese children and adolescents, this would be shortsighted since it relies on the vote-counting approach,[66] an approach that has been shown to be less valid than the meta-analytic approach.[66 67]

Previous systematic reviews with meta-analyses that have focused on the effects of exercise as an independent intervention on BMI as a primary outcome in male and female children and adolescents have reported conflicting findings with five reporting a significant improvement in BMI[68-72] and five others reporting no statistically significant improvement.[73-77] However, nine of the ten suffer from one or more of the following limitations: (1) inclusion of a small number of studies with exercise as the only intervention,[71 73-75] (2) inclusion of non-randomised trials,[68 74] (3) inclusion of children and adolescents who were not overweight or obese.[70 72 74 76 77] Relevant to this application, all ten suffer from both reliance on pairwise versus network meta-analysis, the latter of which incorporates both direct and indirect evidence. In addition, there was an absence of an established hierarchy for determining which types of exercise (aerobic, strength training, or both) might be best for improving BMI based on both direct and indirect evidence.[68-77] To partially address this issue as well as demonstrate feasibility, the investigative team has recently used the network meta-analytic approach to examine the effects of exercise (aerobic, strength training, or both) on BMI z-score in overweight and obese children and adolescents.[78 79] Statistically significant reductions in BMI z-score were found for aerobic exercise and combined aerobic and strength exercise, but not strength training alone (mean, 95% CI: aerobic, -0.10, -0.15 to -0.05; aerobic and strength, -0.11, -0.19 to -0.03; strength, 0.04, -0.07 to 0.15).[79] Combined aerobic and strength training was ranked best, followed by aerobic exercise and then strength training.[79] Consistency in evidence and risk of bias did not differ between direct and indirect studies.[79] It was concluded that combined aerobic exercise and strength training as well as aerobic exercise alone are associated with reductions in BMI z-score.[79] The lack of effect on BMI z-score in the strength training studies may have been the result of increases in lean muscle mass. However, since BMI in kg/m^2 continues to be the most frequently assessed and reported measure of adiposity in both the clinical and public health setting, an examination of such using the network meta-analytic approach is needed. In addition, since all types of BMI measures as well as body weight do not capture changes in body composition (fat mass, percent body fat, etc.), the inclusion of such outcomes, as previously suggested,[79] is also necessary.

Objectives

The primary objectives of the current study are to conduct a systematic review with network meta-analysis of randomised trials to (1) determine the effects of exercise (aerobic, strength training, or both) on adiposity (BMI in kg/m^2, fat mass, percent body fat) in overweight and obese children and adolescents, and (2) establish a hierarchy of exercise interventions (aerobic, strength training, or both) for treating adiposity (BMI in kg/m^2, fat mass, percent body fat) in overweight and obese children and adolescents.

METHODS

Overview

This study will follow the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension statement for network meta-analyses of health care interventions.[80] The protocol for this network meta-analysis is registered in PROSPERO (trial registration number CRD42017073103.

Eligibility criteria

The inclusion criteria for this proposed network meta-analysis will be as follows: (1) direct evidence from randomised trials that compare two or more exercise interventions (aerobic, strength training, both) or indirect evidence from randomised controlled trials that compare an exercise intervention group to a comparative control group (non-intervention, attention control, usual care, wait-list control, placebo), (2) exercise-only intervention (aerobic, strength training, or both), (3) studies lasting ≥ 4 weeks, (4) male and/or female children and adolescents 2 to 18 years of age, (5) participants overweight or obese, as defined by the authors, (6) studies published in any language up to August 31, 2017, (7) data available for BMI in kg/m^2, fat mass or percent body fat.

Studies will be limited to randomised trials because it is the only way to control for confounders that are not known or measured as well as the observation that nonrandomised controlled trials tend to overestimate the effects of healthcare interventions.[81 82] Indirect evidence studies will be limited to randomised controlled trials with at least one exercise arm that participates in either aerobic, strength training, or a combination of aerobic and strength training exercise. Direct evidence studies will be limited to randomised trials that include at least two of the following exercise arms: (1) aerobic, (2) strength training, (3) aerobic and strength training exercise.

For the purposes of this study, exercise, aerobic exercise and strength training will be defined according to the 2008 Physical Activity Guidelines for Americans,[83] defined as movement that is "planned, structured, and repetitive and purposive in the sense that the improvement or maintenance of one or more components of physical fitness is the objective,"[83 84] aerobic exercise as "exercise that primarily uses the aerobic energy-producing systems, can improve the capacity and efficiency of these systems, and is effective for improving cardiorespiratory endurance,"[83] and strength training as "exercise training primarily designed to increase skeletal muscle strength, power, endurance, and mass".[83] Four weeks was chosen as the lower cut point for intervention length based on previous research demonstrating improvements in adiposity over this period of time in 11-year olds.[21]

Participants will be limited to overweight and obese children and adolescents, as defined by the original study authors, because it has been shown that this population is at an increased risk for premature morbidity and mortality throughout their lifetime.[85]

While some research has suggested that studies yielding statistically significant and positive results are more likely to be published in English-language versus non-English language journals,[86] other research has shown this to not be the case.[87] Given the former, studies from both English and non-English-language articles will be included with the latter translated into English by the second author using the freely available web-based Babelfish and Bing translators. For those studies that cannot be translated using Babelfish and/or Bing, professional translation services will be utilized.

Body mass index in $kg{\cdot}m^2$ was included as one of the three primary adiposity outcomes because it is the most commonly used and understood variable by practitioners as well as others and can be easily measured from body weight and height. However, because BMI is an indirect measure of adiposity, fat mass and percent body fat will be included because they are more direct measures of adiposity. The inclusion of fat mass and percent body fat may be especially relevant for studies that include strength training given that decreases in adiposity as measured by BMI may be offset by increases in muscle mass, a secondary outcome that will be coded.

Information sources

The following seven electronic databases will be searched: (1) PubMed, (2) Web of Science, (3) Cochrane Central Register of Controlled Trials (CENTRAL), (4) Cumulative Index to Nursing and Allied Health Literature (CINAHL), (5) Sport Discus, (6) Translating Research into Practice (TRIP) and (7) ProQuest Dissertations and Theses. In addition to electronic database searches, cross-referencing will be conducted by examining the reference lists of previous review articles as well as each included study for potential articles that meet the inclusion criteria. Upon completion of initial searches, the third author will examine the reference list for thoroughness and completeness. Suggested studies will then be retrieved to see if they meet all inclusion criteria.

Search strategy

Search strategies specific to each database will be developed by the investigative team. Major keywords, or forms of keywords to include will be “random”, “children”, “adolescents”, “overweight”, “obese”, “exercise,” “physical fitness”, “body composition”, “fat mass”, “body fat”, “body composition”, “body mass index”, “adiposity”. A copy of a preliminary search strategy using PubMed, including limits, can be found in Supplementary file 1. This search strategy will be adapted for other database searches.

All database searches and article retrieval will be conducted by the second author with oversight from the first author.

Study records

Study selection

All studies to be screened will be imported into EndNote (version X8; New York, NY: Thomson-Reuters; 2016) and duplicates removed electronically and then manually by the second author. A copy of the database will then be provided to the first author for duplicate screening. To minimize selection bias, the first and second authors will select all studies, independent of each other. They will then review their selections for accuracy and consistency. The full report for each article will be retrieved for all titles and abstracts that appear to meet the inclusion criteria as well as those where uncertainty exists. Multiple reports for the same study will be addressed by including the most recently published article and drawing from prior reports, assuming the same methods and sample sizes are reported. Based on previous research suggesting neither a clinically nor statistically significant effect on results, blinding to journal titles, study authors, or institutions of the authors will not be employed during the screening and data abstraction processes.[88] Reasons for excluded studies will be recorded using the following categories: (1) inappropriate population, (2) inappropriate intervention, (3) inappropriate comparison(s), (4) inappropriate outcome(s), (5) inappropriate study design, (6) other. Upon the conclusion of screening, the first and second authors will meet and review their selections. Cohen's kappa statistic (κ) will be used to measure inter-selection agreement.[89] Any discrepancies will be resolved by consensus. If consensus cannot be reached, the third author will serve as an arbitrator. Upon selecting the final number of studies to include, the overall precision of the searches will be computed by dividing the number of included studies by the total number of studies screened after removing duplicates.[90] The number needed-to-read (NNR) will then be calculated as the reciprocal of the precision.[90] A flow diagram that describes the search procedure will be included as well as a supplementary file that includes a reference list of all excluded studies, including the reason(s) for exclusion. Figure 1 illustrates the proposed structure for the flow diagram.

Data abstraction

For this project, Microsoft Excel (version 2016; Redmond, WA: Microsoft Corporation; 2016) will be used to develop comprehensive electronic codebooks that will define the coding process for each of the variables coded. The codebook will be created by the first two authors with feedback from the third author. Consequently, the abstraction of data from the studies in this proposed project should require little subjective judgment on the part of the coder. The major groups of variables to code will include (1) study characteristics (author, journal, year of publication, etc.), (2) participant characteristics (age, gender, height, body weight, etc.), and (3) data for primary and secondary outcomes (sample sizes, baseline and post-exercise means and standard deviations, etc.). Table 1 contains a preliminary list of variables that will be coded. Based on previous research by the investigative team,[79] a codebook capable of including at least 242 items from each study is expected. To avoid data abstraction bias, the first two authors will independently code (dual-coding) all studies to ensure accuracy and consistency. Inter-rater agreement will be assessed using Cohen's kappa statistic (κ).[89] Any disagreement in the items coded will be discussed until mutual agreement is reached. If agreement cannot be reached, the third author will serve as an arbitrator.

Outcomes and prioritization

The primary outcomes in this study will be changes BMI in kg/m^2, fat mass, and percent body fat in overweight and obese children and adolescents. Secondary outcomes will include body weight, lean body mass, waist circumference, waist-to-hip ratio, energy intake, energy expenditure, physical activity level, maximum oxygen consumption (relative and absolute), muscular strength, resting systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, ratio of total cholesterol to high-density lipoprotein cholesterol, non-high density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glycosylated hemoglobin, fasting and non-fasting glucose and insulin.

Risk of bias assessment in individual studies

Risk of bias for included studies will be assessed using the Cochrane Risk of Bias Instrument.[91] Assessment is based on judgments of low, high or unclear risk of bias across six defined domains: (1) sequence generation, (2) allocation sequence concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessors, (5) incomplete outcome data, and (6) selective outcome reporting. A seventh domain, whether participants were exercising regularly, as defined by the original study authors prior to taking part in the study, will also be assessed using the same approach as for the other six domains. As previously recommended, study-level results will reported for each domain according to risk of bias (low, high, or unclear) while the percentage of low, high, or unclear results across each domain will also be reported.[91] This risk of bias approach has been recommended over the use of study quality rating scales given the lack of empirical evidence to support the latter.[82 92 93] Assessment for risk of bias will be limited to the primary outcomes of interest, i.e., changes in BMI in kg/m^2, fat mass, and percent body fat. All studies will be classified as high risk of bias with respect to the category "blinding of participants and personnel" given that it's virtually impossible to blind participants to group assignment in exercise intervention protocols. Based on previous research, no study will be excluded based on risk of bias results.[94]

Data Synthesis

Calculation of effect sizes

The primary outcomes for this study will be changes in BMI in kg/m^2, fat mass (kg), and percent body fat using the original metric. Changes for indirect comparisons will be calculated by subtracting the change outcome difference in the exercise group minus the change outcome difference in the control group. Variances will be computed using the pooled standard deviations of change scores in the exercise and control groups. If change score standard deviations are not available, they will be calculated from 95% confidence intervals (CI) for either change outcome or treatment effect differences as well as pre and post standard deviation values, the latter according to procedures developed by Follmann et al.[95] For direct comparisons, i.e., randomised trials with no control group, the same general procedures will be followed except that the control group data will be replaced with one of the exercise interventions as follows: (1) aerobic minus strength training, (2) aerobic and strength training combined minus aerobic training, (3) aerobic and strength training combined minus strength training. Ninety-five percent CI and *z*-alpha values will be calculated for each outcome from each study. For those studies that include both direct and indirect comparisons, only direct comparison data will be included since a primary purpose of the current meta-analysis is determining which exercise interventions(s) might work best for improving adiposity in children and adolescents. For studies in which adiposity outcomes are assessed at multiple intervention time points, for example, 0, 8, and 16 weeks, only data from the initial and last assessment will be used. If follow-up data are available, results from such will also be analyzed separately to determine the sustainability of changes in adiposity. If any crossover trials are included, treatment effects will be calculated by using all assessments from the intervention and control periods and analyzing them similar to a parallel group trial.[96] While the possibility of a unit-of-analysis error exists as well as studies being under versus over-weighted, this method is believed to be better than alternative approaches, for example, limiting data from the first assessment point or trying to impute standard deviations, especially given the primary and secondary outcomes included and expected distribution of findings,.[96]

Secondary outcomes (body weight, lean body mass, waist circumference, waist-to-hip ratio, energy intake, energy expenditure, maximum oxygen consumption (relative and absolute), resting systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, ratio of total cholesterol to high-density lipoprotein cholesterol, non-high density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glycosylated hemoglobin, fasting and non-fasting glucose and insulin) will be handled using the same approach as for primary outcomes. However, given the different metrics expected and the inability to convert between them, changes in physical activity levels and muscular strength will be calculated using the standardized effect size, adjusted for small sample sizes.[97]

Pooled estimates for changes in outcomes

Network (geometry) plots for each outcome will be used to provide a visual representation of the evidence base with nodes (circles) weighted by the number of participants randomised to each treatment and edges (lines) weighted by the number of studies evaluating each pair of treatments.[98 99] *Contribution plots* for each outcome will be used to determine the most dominant comparisons for each network estimate as well as for the entire network.[98] The weights applied will be a function of the variance of the direct treatment effect and the network structure, the result being a percent contribution of each direct comparison to each network estimate.[98]

Network meta-analysis will be performed using *multivariate random-effects meta-regression models* that can be performed within a frequentist setting, allows for the inclusion of potential covariates, and correctly accounts for the correlations from multi-arm trials.[100 101] A two-tailed alpha value $\leq$ 0.05 and non-overlapping 95% CI will be considered to represent statistically significant changes. Separate network meta-analysis models will be used to examine for changes in each primary and secondary outcome. Potential *covariates* will be examined by (1) conducting simple meta-regression for statistically significant associations between covariates and changes in primary outcomes (BMI in kg/m^2 , fat mass, percent fat), (2) examining for multicollinearity between covariates (r > 0.80), and (3) building a multiple meta-regression model. A list of potential covariates to examine using simple meta-regression is shown in Table 1. While we will include all methods used to assess adiposity, we will also conduct sensitivity analyses to see if results differ according to method of assessment, for example, fat mass assessed using whole body magnetic resonance imaging versus bioelectrical impedance. Secondary outcomes (energy intake and expenditure, physical activity level, muscular strength) will be handled using the same approach. *Transitivity, i.e.,* similarity in the distribution of potential effect modifiers across the different pairwise comparisons for each outcome[102] will include those listed in Table 1. *Inconsistency*, i.e., differences in effect estimates between direct and indirect results for the same comparison,[103] will be checked by assessing differences in treatment effects between direct and indirect effect estimates as well as differences between trials with different designs, for example, two-arm versus multi-arm trials.[101 103 104] However, the probability of inconsistency is considered small given recent research demonstrating that inconsistency was detected in only 2% to 14% of tested loops, depending on the effect measure and heterogeneity estimation method.[105 106] Finally, *prediction intervals* will be used to enhance interpretation of results with respect to the magnitude of heterogeneity as well as provide an estimate of expected results in a future study.[107-109] For network meta-analysis, degrees of freedom (*df)* will be set to the number of studies – the number of comparisons – 1.[109]

Meta-biases

Small-study-effects (publication bias, etc.) will be assessed using comparison adjusted funnel plots.[98] In the absence of small-study effects, the comparison adjusted funnel plot should be symmetric around the zero line.

Confidence in cumulative evidence

Quality analysis of specific pairwise effect estimates in the network meta-analysis will be evaluated using a recently developed modification of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) for network meta-analysis across five domains: (1) study limitations, (2) indirectness, (3) inconsistency, (4) imprecision, and (5) small-study effects.[110] Assessment will be conducted using the same procedures as for study selection and data abstraction.

To establish a hierarchy of exercise interventions for selected outcomes in the current meta-analysis, *ranking analysis,* i.e., the ability to rank all interventions for a single outcome under study, for example changes in BMI in kg/m^2, will be used based on probabilities. However, because the ranking of treatments based exclusively on the probability of each treatment being the best should be avoided given that it does not account for the uncertainty in the relative treatment effects and the possibility for assigning higher ranks for treatments in which little evidence is available, separate *rankograms and cumulative ranking probability plots* will be used to present ranking probabilities along with their uncertainty for changes in primary and secondary outcomes.[98 111] The surface under the cumulative ranking curve (SUCRA), a transformation of the mean rank, will be used to establish a hierarchy of exercise interventions (aerobic, strength, both) while accounting for the location and variance of all treatment effects.[98 111] Larger SUCRA values indicate better ranks for the treatment.[98 111] Interpretation of all rankings will be approached from the perspective of absolute and relative treatment effects.[99]

Software used for statistical analysis

All data will be analysed using Stata (V.14.1; Stata/SE for Windows, version 14.0. College Station, TX: Stata Corporation LP; 2015), Microsoft Excel (version 2016; Redmond, WA: Microsoft Corporation; 2016), and two add-ins for Excel, SSC-Stat (V.2.18; SSC-Stat, version 3.0. University of Reading, United Kingdom: Statistical Services Center; 2007), and EZ-Analyze (V.3.0; EZ Analyze, version 3.0. TA Poynton; 2007).

ETHICS AND DISSEMINATION

This study does not require ethics approval. Findings will be presented at a professional conference and published in a peer-reviewed journal.

CONTRIBUTORS

GAK is the guarantor. GAK, KSK and RRP drafted the manuscript. All authors contributed to (1) the development of the data sources to search for relevant literature, including search strategy, (2) selection criteria, (3) data extraction criteria and (4) risk of bias assessment strategy. GAK provided statistical expertise while RRP provided content expertise on exercise and adiposity in overweight and obese children and adolescents. All authors read, provided feedback, and approved the final manuscript.

REGISTRATION

In accordance with the Primary Reporting Items for Systematics Reviews and Meta-Analyses Protocols (PRISMA-P) statement, this systematic review with network meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on August 23, 2017 (#CRD42017073103).

AMENDMENTS TO PROTOCOL

None to date. If this protocol is amended, the date of each amendment, a description of the change, as well as a rationale for the change, will be provided.

COMPETING INTERESTS

None.

FUNDING

This study is funded by the American Heart Association, Grant #17GRNT33630158 (GA Kelley, Principal Investigator). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the American Heart Association.

DATA SHARING STATEMENT

All data will be available upon request from the corresponding author.

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Table 1. Covariates to examine using simple meta-regression.

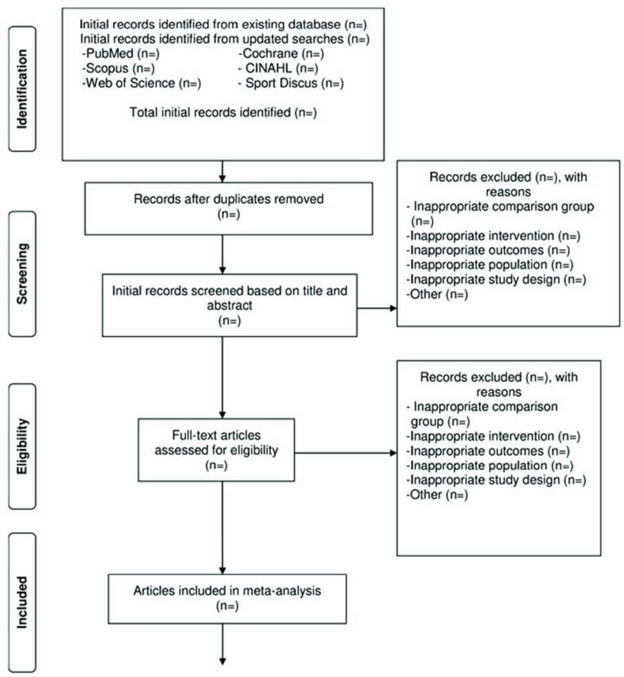
Characteristics	Variable
Study	Publication year, impact factor of journal, country study conducted, type of control group, bias (sequence generation, allocation concealment, blinding of participants & personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting), type of analysis
Participant	Age, gender, race/ethnicity, maturational stage
Exercise	Type (aerobic, strength, both), length, frequency, intensity, duration, total minutes, total minutes (adjusted for compliance), mode, compliance, exercise supervision, setting, number of sets, number of repetitions, rest between sets, number of exercises, type of resistance, equipment used, fidelity (design, training, delivery, receipt, enactment)
Outcome	Baseline values for primary outcomes (BMI in kg/m^2, fat mass, percent fat), method used to assess adiposity, i.e., instrumentation, body weight, lean body mass, waist circumference, waist-to-hip ratio, diet, energy intake, energy expenditure, physical activity level, non-exercise activity, maximum oxygen consumption (relative and absolute), muscular strength, resting systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, ratio of total cholesterol to high-density lipoprotein cholesterol, non-high density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, glycosylated hemoglobin, fasting and non-fasting glucose and insulin

FIGURE LEGEND

Figure 1. Proposed flow diagram to depict the search process.

SUPPLEMENTARY FILE

Supplementary File 1. Preliminary search results in PubMed.



Flow diagram for network meta-analysis.

86x111mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Line #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	**1-2**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	**NA**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	**43; 131-132;394-398**
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	**4-7; 9-12;14-17**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	**387-393**
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	**399-401**
Support:			**404-408**
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	**60-119**
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	**120-126**
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	**133-179**
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	**180-189**
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	**190-198; Supplementary file 1**
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	**201-202; 228-230;378-383**

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	**201-226; Figure 1**
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, duplicate), any processes for obtaining and confirming data from investigators	**227-243**
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources) any pre-planned data assumptions and simplifications	**233-239;244-253;Table 1**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	**244-253**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	**254-272**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	**274-350; 362-376; & Table 1 for 15a-d**
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	**351-354**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	**355-361**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.