PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Exercise and Adiposity in Overweight and Obese Children and Adolescents: Protocol for a Systematic Review and Network Meta-Analysis of Randomised Trials
AUTHORS	Kelley, George; Kelley, Kristi; Pate, Russell

VERSION 1 – REVIEW

REVIEWER	Andrew Jull University of Auckland New Zealand
REVIEW RETURNED	15-Sep-2017

GENERAL COMMENTS	Thank you for the opportunity to review this protocol. It is written to a high standard and addresses almost all the likely questions a reader may raise. The authors have previously undertaken a network meta-analysis of the effects of exercise in overweight and obese children and adolescents with z-BMI as the outcome (published August 2017, but without full citation in the manuscript, possibly because the print verison is not yet available). The proposed network meta-analysis will supplement that information by adding information about the effects of exercise on adiposity in addition to the effects on BMI (as opposed to z-BMI). I have only one major comment and that is the authors propose to not search for unpublished trials on the basis of a paper by van Driel and colleagues showing most unpublished papers were ultimately published, most unpublished papers were of lower quality, and the effort involved in searching for unpublished papers was therefore unjustified. This sole paper used a sample of Cochrane reviews that had included unpublished trials, but does not acknowledge the likely effect that inclusion ultimately prompted publication - that has been my experience with an unpublished trial I included in one of my reviews. Klassen et al (Arch Ped Adol Med 2002;156:474-9) showed that only 59% of trials from major pediatrics meetings 1992-95 were published by July 2000. This publication gap aligns with numerous other studies of different fields and is of particular concern given the differential bias towards publication of positive trials shown by Hopewell et al in a Cochrane methodolgical group review (10.1002/14651858.MR000006.pub3). While unpublished trials may be methodologically weaker than published trials, that does not seem a strong rationale for excluding them if one is attempting completeness of the evidence base, particularly as the unpublished evidence is more likely to be towards the null. Further, sensitivity testing will address any concerns about quality.

	I appreciate the difficulty of finding unpublished evidence, but at least including a search of trial registers via the WHO TRIP database could go some way towards addressing this concern. To not address the need for unpublished evidence will be a major limitation that should be acknowledged. That leads to another much lesser point; the authors acknowledge the possibility of ecological fallacy under strengths and limitations in the abstract, but do not discuss the problem in the paper or point to which ecological fallacy they are raising (I am presuming that it is with regard to the assumption the group average reflects the individual's likelihood). The only other very minor detail is with respect to the use of "BMI in kg m2" throughout the paper whereas the convention I am used to is BMI in kg/m2. Perhaps I need updating instead of the paper, but if it is an oversight, it may stand to be corrected. This will be an infomrative review and I look forward to its completion.

REVIEWER	Amanda Staiano Pennington Biomedical Research Center, USA
REVIEW RETURNED	17-Sep-2017

GENERAL COMMENTS	This is an exceedingly well written and complete protocol, and the use of network meta-analysis coupled with the numerous primary and secondary outcomes will provide an important contribution to our understanding of the effects of exercise (including aerobic vs. strength vs. both) on youths' adiposity. The authors satisfied the PRISMA-P standards. Only one question should be addressed: Why was the beginning date of January 1, 1973, selected?

REVIEWER	Vicente Martínez-Vizcaíno Universidad de Castilla-La Mancha, Health and Social Research Center, Cuenca
REVIEW RETURNED	26-Sep-2017

GENERAL COMMENTS	Authors aim to develop a protocol for Exercise and Adiposity in Overweight and Obese Children and Adolescents. Even if this could be an important contribution to this field of knowledge, I would like to make some comments to the authors. The abstract could be benefited from more international data instead of so many data from to US, since the aim of the study is not restricted to US. I would like to encourage the authors to use PRISMA-P to guide this protocol and mention it in methods section. The authors state: “Studies will be limited to published articles and examined for potential small-study effects such as publication bias”. How are the authors going to determine the potential small-effect of studies?, This should be a posterior criteria for subgroup analysis or sensitivity analysis, but it does not seem a inclusion criteria that should be stated as first point.

	The authors state that: “Unpublished work, defined as master’s theses, dissertations, abstracts from conference proceedings, technical reports, and studies conducted but never reported, will not be included”. This is a statement that should be stated in information sources as complementary information I do not consider that the following inclusion criteria should be stated: “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”. The inclusion and exclusion criteria should be stated before conducting the search, moreover researchers will not use only Pubmed as database. It is not clear how the authors are going to combine the use of Cochrane Collaboration’s tool for risk of bias assessment and the inclusion of one extra criteria not previously validated and not included in this tool. I encourage the authors to exclusively use the Cochrane Collaboration’s tool. Authors should describe how they are going to present risk of bias results, whether they are going to calculate the percentage of items the studies meet or other ways to show the results. This protocol will benefit if authors include an “ethics and dissemination” section in which they could explain the relevance of performing this protocol, how it is going to contribute to this field, and strength and limitations that could provide the development of this protocol to this research field.

REVIEWER	Marion Flechtner-Mors, PhD Ulm University Hospital Center of Medicine Division of Sports- and Rehabilitation Medicine Leimgrubenweg 14 89075 Ulm Germany
REVIEW RETURNED	28-Sep-2017

GENERAL COMMENTS	Summary Hierarchy of exercise interventions on obesity in children and adolescents is not well established. The authors address the topic and they are going to determine the effects of hierarchy of exercise interventions in obese children and adolescents on body mass index and selected measures of adiposity. The authors will use network meta-analysis. All relevant studies from 1983 to 2017 will be included in the envisaged survey. Various appropriate statistical methods are used to provide information about the effects of aerobic, strength, or aerobic and strength training interventions in overweight and obese children and adolescents through network meta-analysis. Primary variables are body mass index, fat mass and percentage of body fat. The authors are aware of the limitations of a meta-analysis. They recognize the selection bias and the limitation of the BMI as a measure of adiposity. BMI does not consider lean body mass and fat mass. However, the protocol is appropriate to clarify the association of exercise and body fat. Further, the study will present the hierarchy of exercise after which the fat mass is influenced. The results of the study may be useful for recommendations on which types of exercise are appropriate for overweight and obese children.

	The results from previous trials on BMI z-score using different exercise interventions have been published. BMI is a rough measure for obesity that does not consider the fat mass, the distribution of fat or the lean body mass. The authors plan to concretize the knowledge of exercise interventions on body fat and body fat distribution. The results will be useful for practitioners. It is striking that recent publications lack data of fat mass and free fat mass, though measurement of these parameters are easily determined by bioelectrical impedance, and which is routinely done in specific studies and by practitioners. Bioelectrical impedance is not the gold standard for measuring body composition. Therefore, from the scientific point of view, the protocol should include fat mass measurement by whole-body magnetic resonance imaging, if available. In regard to secondary outcomes the reader would be interested to know the methods of measuring energy intake and energy expenditure, physical activity level and muscular strength. The introduction is lengthy and should be shortened.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1: Dr. Andrew Jull
Institution and Country: University of Auckland, New Zealand
Please state any competing interests or state 'None declared': None declared

Thank you for taking the time to thoroughly review this manuscript. Based on your suggestions, we believe the manuscript has now been strengthened considerably. To make it easier for you, we have copied your comments below, designated as "C", with our responses after each one, designated as "R". Line numbers refer to those that we have inserted into the manuscript and which correspond exactly with each line. In the revised manuscript, additions and changes also appear using red font, although I don't know if you'll be able to see this or not.

C1. Thank you for the opportunity to review this protocol. It is written to a high standard and addresses almost all the likely questions a reader may raise. The authors have previously undertaken a network meta-analysis of the effects of exercise in overweight and obese children and adolescents with z-BMI as the outcome (published August 2017, but without full citation in the manuscript, possibly because the print version is not yet available). The proposed network meta-analysis will supplement that information by adding information about the effects of exercise on adiposity in addition to the effects on BMI (as opposed to z-BMI).

R1. Thanks so much for the positive feedback. It is greatly appreciated. Also, thank you for noticing the missing page numbers. This manuscript is now published in final form and the page numbers are now inserted. Please see reference number 79.

C2. I have only one major comment and that is the authors propose to not search for unpublished trials on the basis of a paper by van Driel and colleagues showing most unpublished papers were ultimately published, most unpublished papers were of lower quality, and the effort involved in searching for unpublished papers was therefore unjustified. This sole paper used a sample of Cochrane reviews that had included unpublished trials, but does not acknowledge the likely effect that inclusion ultimately prompted publication - that has been my experience with an unpublished trial I included in one of my reviews. Klassen et al (Arch Ped Adol Med 2002;156:474-9) showed that only 59% of trials from major pediatrics meetings 1992-95 were published by July 2000.

This publication gap aligns with numerous other studies of different fields and is of particular concern given the differential bias towards publication of positive trials shown by Hopewell et al in a Cochrane methodological group review (10.1002/14651858.MR000006.pub3). While unpublished trials may be methodologically weaker than published trials, that does not seem a strong rationale for excluding them if one is attempting completeness of the evidence base, particularly as the unpublished evidence is more likely to be towards the null. Further, sensitivity testing will address any concerns about quality. I appreciate the difficulty of finding unpublished evidence, but at least including a search of trial registers via the WHO TRIP database could go some way towards addressing this concern. To not address the need for unpublished evidence will be a major limitation that should be acknowledged.

R2. Good observation. As suggested, we will search the TRIP database as well as the ProQuest Dissertations and Theses database. Along those lines, we have deleted the reference of Van Driel et al. Please see lines 183 and 184.

C3. That leads to another much lesser point; the authors acknowledge the possibility of ecological fallacy under strengths and limitations in the abstract, but do not discuss the problem in the paper or point to which ecological fallacy they are raising (I am presuming that it is with regard to the assumption the group average reflects the individual's likelihood).

R3. Great. And yes, this is what we were referring to. Based on your observation, we now provide the specific information you suggested in the strengths and limitations of the abstract. Please see lines 57 and 58.

C4. The only other very minor detail is with respect to the use of "BMI in kg m2" throughout the paper whereas the convention I am used to is BMI in kg/m2. Perhaps I need updating instead of the paper, but if it is an oversight, it may stand to be corrected.

R4. Thanks for noticing this. We actually had a raised period between kg and m2 but we now realize that it is difficult to see. Based on your observation, we now include the slash sign instead. Please see lines 34, 48, 114, 123, 126, 142, 245, 268, 275, 330, 364 and Table 1 footnotes for this change.

C5. This will be an informative review and I look forward to its completion.

R5. Thank you so much. We are hopeful that the final product will provide a valuable contribution to this global problem and believe that your suggestions will increase the quality of this work.

Response to Reviewer 2: Dr. Amanda Staiano
Institution and Country: Pennington Biomedical Research Center, USA
Please state any competing interests or state ‘None declared’: None declared

Thank you for taking the time to review our manuscript. Based on your suggestion, we believe the manuscript has been strengthened. To make it easier for you, we have copied your comments below, designated as “C”, with our responses after each one, designated as “R”. Line numbers refer to those that we have inserted into the manuscript and which correspond exactly with each line. In the revised manuscript, additions and changes appear using red font, although I don’t know if you’ll be able to see this or not.

C1. This is an exceedingly well written and complete protocol, and the use of network meta-analysis coupled with the numerous primary and secondary outcomes will provide an important contribution to our understanding of the effects of exercise (including aerobic vs. strength vs. both) on youths' adiposity. The authors satisfied the PRISMA-P standards.

R1. Thank you so much for the positive feedback. We greatly appreciate it.

C2. Only one question should be addressed: Why was the beginning date of January 1, 1973, selected?

R2. Good. We used 1973 as the start date based on a preliminary PubMed search in which the first study to screen based on our eligibility criteria was published in 1973. However, based on a suggestion from Reviewer #3, this information has now been deleted. Please see line 30 as well as lines 141-142.

Response to Reviewer 3: Dr. Vicente Martínez-Vizcaíno
Institution and Country: Universidad de Castilla-La Mancha, Health and Social Research Center, Cuenca
Please state any competing interests or state 'None declared': None declare

Thank you for taking the time to review our manuscript. To make it easier for you, we have copied your comments below, designated as "C", with our responses after each one, designated as "R". Line numbers refer to those that we have inserted into the manuscript and which correspond exactly with each line. In the revised manuscript, additions and changes appear using red font, although I don't know if you'll be able to see this or not.

C1. Authors aim to develop a protocol for Exercise and Adiposity in Overweight and Obese Children and Adolescents. Even if this could be an important contribution to this field of knowledge, I would like to make some comments to the authors.

R1. As an NIH-R01 funded Principal Investigator to conduct exercise and meta-analytic research for more than 20 years, the first author thanks you for what appears to be positive feedback.

C2. The abstract could be benefited from more international data instead of so many data from to US, since the aim of the study is not restricted to US.

R2. In the abstract, there is actually no focus on the US. In fact, the first sentence specifically mentions overweight and obesity as a worldwide health problem (see line 23). However, in the Introduction section of the manuscript, we originally included both worldwide information as well as information focused on the US. Because of your concern, and to address Reviewer 4's suggestion about shortening the Introduction, we now focus the information in the Introduction section on worldwide data. Please see lines 61-119 for these deletions.

C3. I would like to encourage the authors to use PRISMA-P to guide this protocol and mention it in methods section.

R3. Actually, we did include the PRISMA Protocol (PRISMA-P) Checklist. It was uploaded and appeared on pages 39 and 40 of the pdf copy that the BMJ Open website produced. An updated PRISMA-P checklist for this revised version is included again. Also, including the reference to the PRISMA-P protocol checklist in the Methods section is not a policy of BMJ Open or any other journal that we know of. Rather, journals ask for this to be uploaded for reviewers to examine, something we did.

C4. The authors state: “Studies will be limited to published articles and examined for potential small-study effects such as publication bias”. How are the authors going to determine the potential small-effect of studies? This should be a posterior criteria for subgroup analysis or sensitivity analysis, but it does not seem a inclusion criteria that should be stated as first point.

R4. You appear to be confused by what should be done here. First, based on recommendations from others, and as stated on lines 349-351 of the original manuscript and now on lines 352 to 354 of the revised protocol, we will use comparison adjusted funnel plots to examine potential small-study effects and as recommended by others for network meta-analysis (see: Chaimani A, Higgins JPT, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. PLoS One 2013;8,10). Second, we refer you to the guidelines developed by others regarding the assessment of small study-effects in meta-analysis (see: Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Br Med J 2011;343:d4002). Briefly, the term small-study effects is now recommended over the term publication bias because asymmetric funnel plots can be the result of factors other than just publication bias. Third, if you look at item #16 of the PRISMA protocol checklist, they specifically recommend an assessment of meta-biases such as publication bias, i.e., small-study effects. Since this is a protocol, it is obviously being described “a priori”as it should be. Fourth, this is the same approach we have used for two previously published protocols in BMJ Open (see: 1. Kelley GA, Kelley KS. Exercise and BMI z-score in overweight and obese children and adolescents: protocol for a systematic review and network meta-analysis of randomised trials. BMJ Open 2016;6(e011258):1-7; 2. Kelley GA, Kelley KS, Callahan LF. Community-deliverable exercise and anxiety in adults with arthritis and other rheumatic diseases: a protocol for a systematic review and meta-analysis of randomised controlled trials. BMJ Open 2017;7(e014957):1-7).

C5. The authors state that: “Unpublished work, defined as master’s theses, dissertations, abstracts from conference proceedings, technical reports, and studies conducted but never reported, will not be included”. This is a statement that should be stated in information sources as complementary information.

R5. Based on a suggestion from Reviewer #1, this information has been deleted from the revised manuscript.

C6. I do not consider that the following inclusion criteria should be stated: “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”. The inclusion and exclusion criteria should be stated before conducting the search, moreover researchers will not use only PubMed as database.

R6. As suggested, we have removed the year 1973. See line 30 as well as lines 141-142.

C7. It is not clear how the authors are going to combine the use of Cochrane Collaboration’s tool for risk of bias assessment and the inclusion of one extra criteria not previously validated and not included in this tool. I encourage the authors to exclusively use the Cochrane Collaboration’s tool.

R7. Actually, the Cochrane Collaboration Risk of Bias Assessment Instrument does allows for an assessment of “Other” sources of bias as determined by the study investigators (see: 1. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011; 2. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J 2011;343:d5928). Therefore, since it is recommended to include such and we believe previous exercise is a potential threat to the results of the proposed study, we have included such.

We will evaluate this seventh domain using the same approach as for the other six domains and now state how this will be assessed on lines 261 and 262.

C8. Authors should describe how they are going to present risk of bias results, whether they are going to calculate the percentage of items the studies meet or other ways to show the results.

R8. As suggested, we now include this information and base our approach as recommended by the Cochrane Collaboration (see: (see: 1. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011; 2. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J 2011;343:d5928). See lines 262-265.

C9. This protocol will benefit if authors include an “ethics and dissemination” section in which they could explain the relevance of performing this protocol, how it is going to contribute to this field, and strength and limitations that could provide the development of this protocol to this research field.

R9. The relevance of this project is justified in the Introduction section of the manuscript (see lines 60-119). The strengths and limitations of this proposed project are listed in the Strengths and Limitations section of the manuscript (see lines 45-58). The dissemination of findings is listed in the Dissemination section of the manuscript (see lines 384-386).

Response to Reviewer 4 (Dr. Marion Flechtner-Mors)
Institution and Country: Ulm University Hospital, Center of Medicine, Division of Sports- and Rehabilitation Medicine, Leimgrubenweg 14, 89075 Ulm, Germany
Please state any competing interests or state ‘None declared’: none declared

Thank you for taking the time out of your busy schedule to review our protocol. Based on your suggestions, we believe the manuscript has been strengthened. To make it easier for you, we have copied your comments below, designated as “C”, with our responses after each one, designated as “R”. Line numbers refer to those that we have inserted into the manuscript and which correspond exactly with each line. In the revised manuscript, additions and changes appear using red font, although I don’t know if you’ll be able to see this or not.

C1. Hierarchy of exercise interventions on obesity in children and adolescents is not well established. The authors address the topic and they are going to determine the effects of hierarchy of exercise interventions in obese children and adolescents on body mass index and selected measures of adiposity. The authors will use network meta-analysis.

All relevant studies from 1983 to 2017 will be included in the envisaged survey. Various appropriate statistical methods are used to provide information about the effects of aerobic, strength, or aerobic and strength training interventions in overweight and obese children and adolescents through network meta-analysis. Primary variables are body mass index, fat mass and percentage of body fat.

The authors are aware of the limitations of a meta-analysis. They recognize the selection bias and the limitation of the BMI as a measure of adiposity. BMI does not consider lean body mass and fat mass. However, the protocol is appropriate to clarify the association of exercise and body fat. Further, the study will present the hierarchy of exercise after which the fat mass is influenced. The results of the study may be useful for recommendations on which types of exercise are appropriate for overweight and obese children.

The results from previous trials on BMI z-score using different exercise interventions have been published. BMI is a rough measure for obesity that does not consider the fat mass, the distribution of fat or the lean body mass. The authors plan to concretize the knowledge of exercise interventions on body fat and body fat distribution. The results will be useful for practitioners.

R1. Thank you for the positive feedback. It is greatly appreciated.

C2. It is striking that recent publications lack data of fat mass and free fat mass, though measurement of these parameters are easily determined by bioelectrical impedance, and which is routinely done in specific studies and by practitioners. Bioelectrical impedance is not the gold standard for measuring body composition. Therefore, from the scientific point of view, the protocol should include fat mass measurement by whole-body magnetic resonance imaging, if available.

R2. Great points. While we listed instrumentation as a potential covariate in Table 1, line 2 of the "Outcome" section of the table, we obviously did not provide enough detailed information about this. Since this is a meta-analysis, we will include all measurements of fat mass and then conduct sensitivity analyses to see if results differ according to method of assessment. Please see lines 333-336 for this additional information.

C3. In regard to secondary outcomes the reader would be interested to know the methods of measuring energy intake and energy expenditure, physical activity level and muscular strength.

R3. Good. Thank you. Similar to the assessment of fat mass and since this is a meta-analysis, we will include all methods used to assess energy intake and expenditure, physical activity level, and muscular strength, and then conduct sensitivity analyses to see if results differ according to method of assessment. Please see lines 336-338 for this important information you've identified.

C4. The Introduction is lengthy and should be shortened.

R4. Based on your suggestion as well as the suggestion of Reviewer #3 regarding the inclusion of US data, we have shortened the Introduction section of the manuscript. Please see lines 60-126.

VERSION 2 – REVIEW

REVIEWER	Andrew Jull University of Auckland New Zealand
REVIEW RETURNED	17-Oct-2017

GENERAL COMMENTS	Thank you for the opportunity to review the revised submission. The authors have satisfactorily addressed the points that I had raised. I look forward to reading the completed review, which will, I hope, answer important questions for the treatment of overweight and obesity. I wish the authors all the best with their endeavour.

REVIEWER	Amanda Staiano Pennington Biomedical Research Center, USA
REVIEW RETURNED	10-Oct-2017

GENERAL COMMENTS	The authors sufficiently addressed all of the reviewers' concerns.

REVIEWER	Dr. Vicente Martínez-Vizcaíno Universidad de Castilla-La Mancha, Health and Social Research Center, Cuenca
REVIEW RETURNED	12-Oct-2017

GENERAL COMMENTS	None

REVIEWER	Prof. Dr. Marion Flechtner-Mors Ulm University Hospital Center of Medicine Division of Sports and Rehabilitation Medicine Ulm, Germany
REVIEW RETURNED	28-Oct-2017

GENERAL COMMENTS	The results of the study will be useful for practitioners. The results of the study will be a tool for combat epidemic obesity.