PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Dietary and/or physical activity interventions in women with overweight or obesity prior to fertility treatment - Protocol for a systematic review and individual participant data meta-analysis
AUTHORS	Evans-Hoeker, Emily; Wang, Zheng; Groen, Henk; Cantineau, Astrid EP; Thurin-Kjellberg, Ann; Bergh, Christina; Laven, J; Dietz de Loos, Alexandra; Jiskoot, G; Baillargeon, Jean-Patrice; Palomba, Stefano; Sim, Kyra; Moran, LJ; Espinós, Juan J; Moholdt, Trine; Rothberg, Amy E; Shoupe, Donna; Hoek, Annemieke; Legro, Richard S.; Mol, Ben; Wang, Rui

VERSION 1 – REVIEW

REVIEWER	Hong, Xiang Southeast University, public health
REVIEW RETURNED	15-Jun-2022

GENERAL COMMENTS	This is an important system review. The findings would help to inform treatment strategies for overweight/obese infertility women. Especailly the 'minimun amount of weight loss', it is an interesting index with great clinical significance. So I suggest the main objective of this meta-analysis should found this optimal range, no just to explore the association between intervention and fertility treatment outcome. In addition, some suggestions are as follow: 1. The main sources of the heterogeneity are the different types of intervention strategy. The authors just simplely divide the intervention strategy into three types: dietary, physical activity, their combination. This limitation needs to be recognized and more stratified analyses should be performed when possible. In this case, the 'weight loss' index is of great significance. 2. line 227. Non-linear association is an important exploration, should state tbe specific method you want to use; 3. line 217. What is the 'appropriate imputation method'? should be clear. 4. The original analysis from RCT data would based on Intention-To-Treat or Per-Protocol, you should clearly state which one the meta-analysis would take?

REVIEWER	Lee, Chyi-Long Chang Gung Memorial Hospital
REVIEW RETURNED	20-Jun-2022

GENERAL COMMENTS	1. Protocol paper completes with a meaningful result 2. Suggest P.9 cardiometabolic outcomes should include pre-intervention data

REVIEWER	Gibreel, Ahmed
	Mansoura University, Obstetrics and Gynecology Department
REVIEW RETURNED	23-Jun-2022

GENERAL COMMENTS	This is a well written protocol addressing the role of physial therapy and nutritional intervention prior to fertility treatment. Could the authors clarify in doing the senstivity analysis would studies with low risk of bias mean low risk in all domains or certain ones?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Xiang Hong, Southeast University
Comments to the Author:
Q1. *This is an important system review. The findings would help to inform treatment strategies for overweight/obese infertility women. Especially the 'minimum amount of weight loss', it is an interesting index with great clinical significance. So I suggest the main objective of this meta-analysis should found this optimal range, not just to explore the association between intervention and fertility treatment outcome.*
Response: Thank you for the suggestion. While we appreciate the clinical importance of minimum amount of weight loss, this measure is essentially a post-randomisation measure, which should not be the primary focus of an individual participant data meta-analysis of randomized trials. In addition, the usefulness of such a concept would depend on our findings in objective 4 "to explore the association between the magnitude of pre-conception weight change and reproductive and perinatal outcomes." If the association is not found, there will be no "minimum amount of weight loss". Therefore, we propose to keep the objectives as they are, without adding 'minimum amount of weight loss', to prevent overstatements. Therefore, we have not made this change.

In addition, some suggestions are as follow:
Q2. *The main sources of the heterogeneity are the different types of intervention strategy. The authors just simplify divide the intervention strategy into three types: dietary, physical activity, their combination. This limitation needs to be recognized and more stratified analyses should be performed when possible.*
In this case, the 'weight loss' index is of great significance.
Response: Thank you. We have now acknowledged this as a limitation in the discussion. It is likely that more stratified analyses will result in very few studies per subgroup, which will not provide useful evidence. It now reads: "Meanwhile, we acknowledge that the classification of intervention type can only be limited to broad categories in this IPDMA." (Page 16, Line 261-262)
In addition, "Magnitude of weight loss (or BMI points change)" was already included in the treatment-covariate interaction analysis in the original submission. Therefore, no further change was made regarding weight loss index.

Q3. *line 227. Non-linear association is an important exploration, should state the specific method you want to use;*
Response: Thank you. We have added the method by which we are planning to use to handle non-linear association. It now reads: "Non-linear association will be explored using restricted cubic spline according to current practice" Page 13, line 230

Q4. *line 217. What is the 'appropriate imputation method'? should be clear.*
Response: Thank you. We have rephrased the sentence as "Missing data in each study will be dealt with separately using multiple imputation when missing at random assumption is not violated."

Q5. *The original analysis from RCT data would based on Intention-To-Treat or Per-Protocol, you should clearly state which one the meta-analysis would take?*
Response: Thank you. In our original submission, we stated "The main analysis will be based on the intention-to-treat principle" (Line 210) and one of the sensitivity analyses was "women adherent to the intervention (as per-protocol analysis)"(Line 236). Therefore, no change was made in this revision.

Reviewer: 2
Dr. Chyi-Long Lee, Chang Gung Memorial Hospital
Comments to the Author:
Q6. *Protocol paper completes with a meaningful result. Suggest P.9 cardiometabolic outcomes should include pre-intervention data*
Response: Thank you for the compliment. Pre-intervention cardiometabolic data will be reported as baseline information instead of outcome data. As Table 1 in page 9 refers to outcomes only, we did not make further changes.

Reviewer: 3
Dr. Ahmed Gibreel, Mansoura University
Comments to the Author:
Q7. *This is a well written protocol addressing the role of physical therapy and nutritional intervention prior to fertility treatment. Could the authors clarify in doing the sensitivity analysis would studies with low risk of bias mean low risk in all domains or certain ones?*
Response: Thank you for your kind assessment. We will perform sensitivity analysis with studies with overall low risk of bias according to RoB 2 assessments. We have added "overall" in line 234.

VERSION 2 – REVIEW

REVIEWER	Hong, Xiang Southeast University, public health
REVIEW RETURNED	05-Sep-2022

GENERAL COMMENTS	The authors have addressed my concerns.