Wednesday, 03 May 2017

Response to the Editors' and peer-reviewers' comments

Comment	**Response** *(pages and para in revised manuscript, simple mark-up mode)*
Editors	
1. The title should make it clearer that the paper is mostly looking at diet and activity interventions aimed at reducing weight in pregnant women.	Thank you. We accept this suggestion and have revised as *'Effects of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: Individual participant data (IPD) meta-analysis of randomised trials'*
2. As presented, the paper is not going to be of much help to clinicians who see obese pregnant women. Can you improve on this?	We have taken into account this request, and have assessed the differential effects of intervention according to BMI for individual outcomes, in addition to our previous analysis on outcomes such as gestational weight gain and composite outcomes. We have also elaborated further in the discussion section on relevance to clinical practice.
3. Can you be more specific about interventions and maybe decouple the composite outcomes so actions can be seen on an IPD level? There seems little point in using individual data if it is going to be lumped into composites, although we do appreciate the rationale behind this decision as well as the process used to agree on the composition of the outcomes.	In addition to providing the overall effects of interventions for the composite, we have previously provided (and now updated) the effect sizes of overall, and individual interventions for individual outcomes. Further to the Board's suggestions, we have decoupled the composite outcomes, and undertaken additional analysis to assess if there are any differential effects of interventions according to Body Mass Index. This is provided in methods follows *'We additionally evaluated whether there are any differential effects of interventions for individual complications according to the BMI (normal, overweight, obese).'* (page 13, para 3)
4. We would like to see the contributions of the authors listed. All authors should have read the paper with track changes prior to submission to comply with COPE.	We have provided details of author contributions. All authors have read the paper and provided input in email body or as track changes.

5. The major reason given for carrying out this IPD is to test if the effect seen varied by subgroups. The paper states that it did not, but the analysis and the presentation of these is not entirely transparent.	We have provided additional details in revised manuscript as follows Methods: *'This produced summary estimates and 95% confidence intervals (and sometimes 95% prediction intervals) for the intervention effects and the interactions (subgroup effects).'* (page 14, para 23 - 25) Results: Previously our Table 1 provided details of the differential effects for primary outcomes. We have now also reported these findings in the results section of the manuscript under the subheading 'Differential effects in subgroups': *'We observed no strong evidence of differential subgroup effects for either maternal composite outcome according to baseline BMI (treatment-covariate interaction 1.00, 95% CI 0.98 to 1.02), age ………..(Table 2b). A similar lack of differential effect was observed for composite offspring outcome in mothers grouped according to baseline BMI (interaction 0.98, 95% CI 0.95 to 1.00), ………………. The findings did not change for maternal and offspring outcomes when BMI and age were analysed as continuous instead of categorical variables."(*page 19-20, para 15 – 26, 1 – 2).'
6. As one of the main objectives of this IPD was to assess the effects of the intervention in different subgroups, this analysis should be highlighted in the Methods section and expanded slightly. Currently it is only described in the last sentence of the second paragraph of the Data Analysis section: "To assess potential intervention effect modifiers, we extended the aforementioned models to include interaction terms between participant-level covariates and the intervention (i.e. treatment-covariate interaction terms)." Consider placing in a different paragraph as well as expanding how this was reported/presented in the Results section. This paragraph could also include a description of how the categories/subgroups were selected.	We have now provided additional details to addressed this comment in methods, results and discussion sections as below, including the rationale behind the choice of subgroups. Methods: *'A two-stage IPD meta-analysis was used to obtain summary estimates of the subgroup effects (interactions) of interest, which compared differential effects of interventions across the primary outcomes. We additionally evaluated whether there are any differential effects of interventions for individual complications, according to the BMI (normal, overweight, obese).*' (page 13, para 3) Results: Please see our response to comment 5. Discussion: *'The subgroups were chosen in response to the National Institute for Health and Care Excellence's (NICE) call for assessment of the effectiveness of lifestyle interventions in pregnancy, for specific groups of women considered to be at high risk of complications,. ……'* (page24, para 1 - 3)

7. The use of composite outcomes could be problematic if one of the multiple ones included dominates (i.e. is more prevalent). Can you tell us more about this?	No single maternal or offspring component had a disproportionately high prevalence compared to other components in maternal or offspring composite. Of the maternal composite outcomes experienced in both groups (3733 events) the individual components were as follows: gestational diabetes (1155 events), hypertensive disease (855 events) Caesarean section (3031 events), and preterm delivery (677 events). For the offspring composite (1958 events) there individual components were: stillbirth (20 events), SGA (1341 events), LGA (1503 events), and admission to NICU (581 events).
8. The search is about a year old now. We'll leave it to you to decide how to handle that, and recognise that we have partly contributed to this.	We have now updated the search and identified 20 studies (4995 women). This has resulted in reanalysis of the results, with no qualitative changes in direction of effect.
9. In case the paper has been to another journal before coming to us, we would encourage you in line with the ICMJE recommendations to share the correspondence and any reviewer reports with us, in order to share expertise and improve the overall peer review process.	We had previously submitted the paper to Lancet, and received a communication requesting our submission to Lancet Diabetes and Endocrinology. We subsequently also received an email from the Editor of the Lancet Diabetes and Endocrinology, requesting us to submit the paper with his journal (emails attached below). However, we decided to submit our work to BMJ, a generalist paper, since we feel our findings are relevant to the wider medical community.

Comment	Response *(pages and para in revised manuscript, simple mark-up mode)*
Reviewer 1	
10. Participants are adequately described. The inclusion and exclusion criteria for the interventions need to be more detailed. Do “lifestyle” interventions include stress management interventions if these are part of a multi-component intervention addressing diet+/PA/Sedentary Behaviour?	In response to the reviewer’s comment we added following clarification in the methods section: *”As the mixed intervention we classified any complex, multi-component interventions targeting women’s nutrition, level of physical activity, and associated with them habits and behaviour. “* (page 12, para 1 - 3)
11. There needs to be consistency in intervention definition which is variously described for example as “diet and PA based interventions” – p 12 Line 20, `’lifestyle interventions” p 12 Line 42, “interventions based on diet and/ PA – p, 13 Line 42 – which presumably is the correct version, “diet and lifestyle based interventions” p29, L 12; “lifestyle interventions” p29, L 23.	Thank you. We have now consistently used the terminology ‘diet and physical activity based interventions’ throughout the paper.
12. Methods These are mainly adequately described. The study is reported in line with recommended guidelines. Main outcome measures: difference in gestational weight gain and differences in composite maternal and composite infant outcomes. Secondary outcomes are individual maternal and offspring complications.	We thank the reviewer for these comments.
13. The composite outcomes were determined by a two-round Delphi survey previously published. Is pre-term birth more likely an infant outcome? A definition of pre-term delivery needs to be given as all other variables are defined.	We decided to report preterm delivery under maternal outcomes, as we considered any effect of the intervention on mother’s body to be classed as maternal outcome. We have now defined preterm birth as follows in methods section: "preterm delivery (before 37 weeks of gestation) …" (page 12, para 19 - 20)
14. Discussion. This seems rushed and could be elaborated more fully especially in the light of previous literature. The conclusion needs to be rewritten to be more specific in terms of its importance and implications for antenatal care.	We have now elaborated further on the discussion, particularly focussing on the role of central repository, implications of the findings for gestational weight gain, and maternal and offspring outcomes (page 24 - 27)
15. What this study adds needs to be revised (see below) P24 L10. Suggest replacing “with a much stronger evidence for…..” by with a statistically significant reduction in gestational diabetes”.	We have accepted this suggestion and revised as follows ‘Addition of non-IPD to the IPD meta-analysis resulted in significant reduction in gestational diabetes.’(page 26, para 3).

16. P26 Lines 16-18. This sentence needs to be reworded as the authors did not examine the effects of the individual intervention components.	We have evaluated the overall effects of individual interventions on gestational weight gain, and individual maternal and offspring complications. Results are provided in Table 3.
17. P27 Line 27. The word diabetes needs to be added after gestational	We have now revised as follows *'in gestational diabetes and type 2 diabetes,'* (page 27, para 2)
18. P27 Line 36: Whether magnitude of benefit…..varies………needs……	This sentence has been removed in the revised manuscript.
19. P27 Line 41: insert "in those countries" after particularly	We have now modified as follows *'particularly in those countries'* (page 28, para 16)
20. P27 Line 50: "needs assessment" suggest replacing with "needs to be assessed"	We have now modified as follows *'mother and child needs to be assessed'* (page 28, para 12)
21. Referencing- content is up to date and relevant but needs to be fully revised to be consistent in style and formatting e.g references 1,2,12, 16, 21, 38 etc	We have ensured that the referencing is consistent in style and formatting in the revised manuscript.
22. Abstract: Primary and secondary outcomes need to be stated.	We have taken into account this suggestion and revised in the abstract as follows '*We synthesised the evidence on the overall, and differential effects of interventions based on diet and physical activity, primarily on gestational weight gain and composite maternal and offspring outcomes, according to women's body mass index, age, parity, ethnicity and pre-existing medical condition; and secondarily on individual complications.*' (page 7, para 1)
23. Other: There are a number of additional grammatical and / typographical errors: P14 L 57, P15 L47 Delete the word "the", Use comma for thousands e.g p22 Lines 48 and 50,: 3,719; 11,666 and in tables to improve readability	The manuscript has been corrected for any grammatical or typographical errors where necessary. We have added the comma after thousands in the manuscript and in Tables.
Reviewer 2	
24. I believe that the use of composite outcomes is a necessity to gain knowledge of rare adverse events. The strength of using a composite outcome is that real outcomes might be included and not only proxies. Unfortunately, I do not gain access to the Delphi analysis done to identify the composite outcomes. The outcome of this is, however, also the major shortcoming of this study.	The rationale for the choice of composite outcomes in provided in this paper, and also in our published paper Rogozińska et al. Development of composite outcomes for individual patient data (IPD) meta-analysis on the effects of diet and lifestyle in pregnancy: a Delphi survey. BJOG 2016. We assessed the effects of overall, and individual interventions such as diet, physical activity and mixed intervention, on separate maternal and offspring components of the composite outcomes

	to inform clinicians and parents. Furthermore, in response to the Editors' comments, we have assessed if the effects vary according to the BMI of the mothers for these individual outcomes. We believe that this approach strengthens the paper.
25. As a clinician, an advisor for the patient, most important maternal outcomes to avoid by lifestyle advice should include shoulder dystocia, venous thromboembolic events, anal sphincter tears, hypertension and GDM.	The individual components of the composite outcome, which were considered to be important were chosen by a pre-defined process. We agree with the reviewer that the above-mentioned outcomes were important. We did not include them for the following reasons: They were not the top four critical outcomes selected by the Delphi panel, and very few studies reported this outcome. Therefore inclusion of these components in the composite, would have severely limited our ability to robustly assess the effects on maternal outcomes, due to the extremely small sample size. We have acknowledged the importance of the suggestion provided by the reviewer in our Discussion as follows *'There is a need to develop a harmonised core outcome set for future reporting of clinical trials in this area, to maximise the meaningful interpretation of published data. This is particularly relevant for rare but important outcomes such as shoulder dystocia, birth trauma and venous thromboembolic events.'* (page 28, para 2)
26. In the newborn composite outcome the authors included both SGA and LGA. When doing a lifestyle intervention with diet and exercise the major effect will be to lower fetal/newborn weight. We know that with lower maternal weight gain, there will be lower newborn weight. By including both SGA and LGA in their composite outcome, the authors restrict the possibility to show this important effect	While it is possible that the reduction in gestational weight gain may be associated with lowering of fetal weight, the magnitude of such a reduction may not necessarily result in an increase in SGA babies. We assumed that any beneficial effect on weight gain will be in the same direction, i.e. reduction in extremes of birth weight (SGA and LGA). Furthermore, both SGA and LGA babies are at increased risk of admission to the neonatal intensive care unit, one of the components of the composite outcome. The proportion of women with SGA and LGA babies were similar, and the effects of interventions on these individual outcomes were not significant. We therefore feel, that the masking of the intervention effect by the use of composite outcome is low.
27. A more relevant and more powerful analysis to show this difference would be to compare difference in expected weight/	Our previous published aggregate meta-analysis had shown a very small reduction in newborn birth weight. However, this was not considered to be an

birthweight either in grams (as the maternal analysis) or by newborn weight deviation (birthweight minus expected weight/birth weight	important outcome by the Delphi panellists, and hence we did not provide the details.
28. SGA is usually used as a proxy for fetal growth restriction. In this paper lifestyle intervention aim to lower the maternal and fetal increase in weight to lower adverse outcome. In a study like this, SGA should not be an adverse outcome.	SGA was considered to be a critically important outcome by the Delphi panel. We were cautious in assuming a presumed direction of effect with the intervention prior to the study as suggested by the reviewer due to biases in published literature.
29. Further, for me it seem adequate to correct SGA and LGA for gestational age at delivery against a standard/reference. However, to adjust for maternal BMI and parity is partly taking away the differences you aim for	We have used the method currently used in mainly NHS units in the UK, to provide estimates that are generalisable and relevant to current practice.
30. In Lifestyle advice involving exercise, maternal weight/BMI is not a good outcome variable due to redistribution of fat and muscle tissue. I would expect the newborn weight differences to be more pronounced and to be the main single newborn outcome variable.	If there was any redistribution of fat and muscle tissue due to pregnancy, we expect these changes to be equally distributed in the intervention and control group. We therefore consider the inherent bias with this approach to be not large.
31. The authors state this in the end. “There is a need to develop a harmonised core outcome set for future reporting of clinical trials in this area, to maximise the meaningful interpretation of published data.”	This is a statement by the reviewer. No action required.
32. After defining Individual Participant Data by IPD this should be used in the paper	We have changed Individual Participant Data to IPD after the initial introduction of the abbreviation on page 10.
33. It is not easy to understand the reason for non-IPD studies. This should be written more transparent	We have provided this detail in the Discussion as follows *‘In a high priority area such as obesity and weight gain in pregnancy, there has been a rapid increase in the number of published studies, with at least 10 trials published per year since 2011, and 16 published in 2016. We sought to maximise the information needed to inform the findings by combining study-level data from non-IPD studies to the IPD meta-analyses; the conclusions appeared to be robust for nearly all outcomes.’* (page 25, para 1)
34. The authors had not been clear with why they used 20 years as age-categorization. The is used without explanation and it seem to be a post-hoc definition	The 20 years cut off was selected a priori as evidenced in our protocol and analysis plan. We have now clarified our rationale behind the choice of this variable in the methods section as follows ‘*We chose 20 years to be the cut-off for age, as it allowed us to assess the effect of intervention in*

	teenagers, where pregnancy may alter normal growth processes and increase their risk of becoming overweight or obese.[117] Adolescent mothers also retain more weight postpartum than mature control subjects.' (page 24, para 1)
35. The paper may have a more informative headline. Statistics seem adequate, but I would recommend that someone used to IPD analysis to review it	We have now revised the title to 'Effects of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: Individual participant data (IPD) meta-analysis of randomised trials'
36. Conclusion: It is a good paper that adds to our knowledge and will be a reference. However, I believe that the study will underestimate the true differences. An analysis of differences in newborn weight /gestational weight by a growth standard would add even more.	We thank the reviewer for the positive comment on the importance of our work. By assessing the effects on clinical outcomes considered to be critically important by two Delphi surveys, we believe our findings are relevant. We have not identified evidence of significant changes in extremes of fetal weight such as SGA and LGA, which are associated with complications in the offspring, than a continuous measure of fetal weight alone.