PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Towards Prepared mums (TOP-mums) for a healthy start, a lifestyle intervention for women with overweight and a child wish: Study protocol for a randomised controlled trial in the Netherlands
AUTHORS	Timmermans, Yvon; van de Kant, Kim; Reijnders, Dorien; Kleijkers, Lina MP; dompeling, edward; Kramer, Boris; Zimmermann, Luc JI; Steegers-Theunissen, Régine; Spaanderman, Marc EA; Vreugdenhil, Anita

VERSION 1 – REVIEW

REVIEWER	Annick Bogaerts KU Leuven, Belgium
REVIEW RETURNED	10-Apr-2019

GENERAL COMMENTS	Thank you for revising this study protocol entitled “Towards Prepared mums (TOP-mums) for a healthy start, a lifestyle intervention to reduce overweight and smoking in women with a child wish: Study protocol for a randomised controlled trial”. Maternal overweight and obesity is increasing worldwide, and represents a considerable health burden for the mother and her child. This study protocol of a preconception RCT represents a valuable and innovative study considering the association between preconception health (i.e. overweight & smoking) and health of future generations. Preconception lifestyle interventions are upcoming and highly needed to develop practice guidelines. The added value here is the use of body tissues to also study the mechanisms behind the intergenerational transmission of diseases. In general, a this moment, I miss a thorough description of the study setting including the recruitment strategy. Some outcomes to be measured are reported very clear and profound, while others are rather consized and reported superficial/unclear. The title is focusing on smoking reduction, unfortunately this is meant to be a secondary outcome according to the protocol and sounds therefore a bit strange. I suggest to make this more clear in the title. Abstract: Outcomes : health of mother and child, can this be made more clear what is meant here? You choose PPWR up to 6 weeks as primary outcome while you plan to run the trial up to 12 months after delivery? Can you comment on this in the protocol? Body tissues will be stored, does this mean that you don’t want to use it for analysis in this protocol ? I miss details about collection, storage and analysis of these body tissues. Secondary outcomes: you are collecting many many variables to be used as confounders, my concern here is, if you have only

	approximately 15-16 women per stratum, what about type I and type II errors? Introduction: Second para : I suggest to put the info regarding smoking effect together (first and last sentence); try to use more recent references as the number 9 and 10 are more than 10 year old and we now have more strong and recent papers f.e. the Goldstein et al. JAMA paper about associations between BMI, GWG and outcomes. Methods: Randomisation : you make strata for OW, OB & smokers, this means that you create 4 strata with approx.. 15 women per stratum. How do authors cope with issues of power here? How do authors exclude women who are mentally disabled? Recruitment strategy is rather superficial and not really clear to me. How and where are they going to reach 'gynaecologists', 'midwives', 'GP's' and what is meant by Youth Healthcare Division? Geographical region, number of healthcare provider, number of deliveries a year in this region,…. What kind of magazines and lay press is meant, how are authors going to organize this? What is the suspected number and timeframe of this type of recruitment? Please make more clear. Sample size: why do authors target a mean difference in weight from baseline (time of recruitment?) to 6 weeks postpartum? Can you comment about your rationale for this please? From a recent own analysis (Bogaerts et al. midwifery 2016, postpartum weight trajectories) we know that only 1 in 5 women reach prepregnancy weight 6 weeks after delivery, meaning that 80% still has additional weight from their gestational weight gain, besides, nearly 4 in 10 still had more than 5 kg weight in excess. What does the endpoint of 6 weeks pp mean in relation to the effect of your preconception lifestyle intervention? Please make this more clear here? Procedure: How and when will potential participants be screened for eligibility? Can authors be more precise here? You write : 'The informed consent procedure enables follow-up after discontinuation of the RCT in these women', make clear why you need this? Care as usual : can you explain what this means here? Try to be more precise what this means during 'usual' preconception care (GP, MW, Gyn, Youth Hc) Lifestyle intervention: • can you comment on the results from your earlier qualitative study as I can't find a ref to look into the details of these results ? Who will be that personal coach? Will they be trained and if so, by whom ? • eating disorders : how are you going to diagnose this? Who will provide the psychological guidance for four months , two to three times a week? How do you register the adherence and compliance for this guidance? • Who is going to execute the postpartum consultations to support breastfeeding including the dietary advice?

	• Who will be the trained professionals for enhancement of the physical activity? Are they members of the research team? Do you hire them? Please be more precise here? • Will the peadiatric physiotherapist be a member of the research team? Where will he/she be working regarding accessibility for the mothers/babies? Do mothers receive incentives for all these efforts? • Is the lifestyle coach trained in motivational interviewing to support women to quit smoking? Can you clarify this ? • Where will study visits take place? • Why do you calculate gestational weight gain up to 36 weeks and not at the last prenatal consult or at delivery (if possible)? • Can you comment on the use of the double labelled water technique with water labelled with deuterium to measure the BMI ? How are you going to organize this in pregnant and postpartum women? • Which guidelines will be used to determine gestational diabetes, hypertension,… please be clear and transparent here? Are they the same in each site? • Specify your rationale to measure pulse wave velocity and retinal vascular images related to preconception health and impact in next generations? • Sample collection (biomarkers) : the collection and storage of microbial flora, placental tissue and breast milk is reported rather superficially : when exactly and how are the authors going to collect f.e. breastmilk, vaginal an orals swabs ? This part seems rather a list of items to be collected. I miss the rationale behind as well as a clear pathway about the how and the why. Can you comment in the state of the art regarding the possible influence of these biomarkers related to you primary (and secondary) outcome(s) ? Minor remarks: Re Legend for Figure 1: the marked sentence below sounds a bit contradictory to the listed possible impact behind it (a,b,… = formulated in a negative way), I suggest to reformulate this sentence. ".. The effects of lifestyle improvements in this episode can impact health of the entire life span: a) longer time to conception; b) higher risk of pregnancy complications such as gestational diabetes mellitus, gestational hypertension and preeclampsia; c) unfavourable foetal programming by epigenetic processes modulating gene transcription, and by transmission of an unfavourable composition of microbial flora from mother to child; d) higher risk of birth and neonatal complications such as operative delivery, small and large for gestational age, preterm birth and admission to the neonatal intensive care unit; e) higher risk of obesity and pulmonary diseases such as wheezing and asthmatic disease; f) higher risk of chronic diseases such as diabetes mellitus type 2, cardiovascular diseases and dyslipidaemia; g) higher premature mortality rate.

REVIEWER	Rebecca Painter Amsterdam University Medical Centres I may be collaborating with the authors on a future project. We have not yet applied, but are tentatively discussing this possibility
REVIEW RETURNED	06-May-2019

GENERAL COMMENTS	Review

	Towards Prepared mums (TOP-mums) for a healthy start, a lifestyle intervention to reduce overweight and smoking in women with a child wish: Study protocol for a randomised controlled trial Timmermans et al BMJ Open May 2019 General comments This manuscript describes the protocol for a preconception lifestyle intervention study. There are few of these lifestyle intervention studies available at present. The few that have been conducted have been found to be largely ineffective in improving perinatal outcome (systematically reviewed by Lan et al in 2017-please add this essential paper to your references), the majority of the existing studies discontinued the intervention upon conception, and were carried out in a group of subfertile women. Similarly, studies targeting women in pregnancy often can only commence recruiting around the mid trimester, which may explain their limited effects. The proposed study, which continues the preconception intervention into and beyond pregnancy, and targets the general population, therefore takes a much needed and valuable approach, for which the authors should be commended. My comments, outlined below, are mainly encouragement to be more detailed and specific about the study protocol. My concerns for the success of this study's chances of success centre around the time investment asked of all participants, in particular the intervention group. The other concern is the lack of ability for the study to show any differences between the usual care and the intervention group due to the small sample size and possible opposing effects of the interventions aimed at smokers and at obese women. Both of these need more attention in the protocol. Throughout the manuscript, the text could benefit form English language editing. Examples in the abstract include 'Lifestyle interventions may have been not multidisciplinary and customized enough' could be rephrased to ' Lifestyle interventions may not have been sufficiently multidisciplinary or customized'. Other examples include: '….potentially more sufficient….' could be rephrased '…may potentially be better able to achieve…' and '..pregnancy wish..' could be rephrased to ' …who plan to conceive…'. Abstract The abstract states that the study aims to evaluate the effect of a lifestyle intervention on weight change, and health outcomes in mother and child. However, the study is grossly underpowered to look at the majority of outcomes that are mentioned. I would suggest rephrasing the aims to include only realistically achievable goals. Mentioning the intended sample size would benefit the abstract. Strengths and Limitations Add small sample size to the limitations. Introduction

	There is a little inconsistency in the introduction, where smoking and obesity are married under the heading 'unhealthy lifestyle' and the authors subsequently state in line 48-52 that an unhealthy lifestyle can increase the risk of hypertensive disease, preeclampsia, gestational diabetes. To my best knowledge these are all factors that are increased by obesity, and are in fact lower among smokers. Please rephrase this segment to better reflect the differential effects of maternal smoking and maternal overweight/ obesity. The figure does not mention pregnancy loss: this needs adding. There seem to be two names in the paper: Top mums and TOP MAMA. This is confusing. Please align names throughout the manuscript. Line 55 states that LGA is an example of reduced foetal wellbeing. I would disagree with that. I think the authors a referring to the fact that maternal obesity increased the chance of poor perinatal outcome. Please rephrase. Study design Please add minimum and maximum block sizes. Setting and study population The inclusion criteria mention nothing about smoking. Only women with a BMI >=25 kg/m2 seem to be eligible. This is not consistent with the introduction and the abstract. Are any language restrictions applied (eg: only women who are able to read and write English and/or Dutch). Are any limitations applied in terms of women's eligibility if their pregnancy test is already positive when they first present for randomization? Are limitations applied to the population (eg are women in fertility clinics eligible?)- what repercussion does participation have on their treatment at the fertility clinic. Please add this information to the draft. Are women eligible for the study in subsequent pregnancies? Eg after a miscarriage or term birth, can they be randomized again? Recruitment Are potential study participants to complete give their informed consent in writing? Please add. Sample Size This section mentions information that is not relevant to the sample size calculation. None of the studies quoted here actually report on postpartum weight differences. Furthermore, it is unclear whether the drop-out rate is realistic and whether it has been applied to extend sample size or not. Based on the literature, 44% drop out could be broken down into 15-20% early pregnancy loss/termination and 10% not achieving pregnancy within 1 year. The additional 15-20% I assume are women that fail to participate in the full lifestyle programme? Or are they women that do not attend 6 weeks postpartum visit? If indeed it refers to women who have not completed the programme, it is a conservative estimate based on other studies in preconception (eg Mutsaerts et al NEJM). Please specify/ break down these percentages. Also, it is interesting to know whether the authors plan to exclude those who fail to follow the lifestyle programme from intention to treat analyses, which is insinuated if

	they are taken into account in the power calculation- this could be included in a section on statistical analysis plan (at present no such section is included- could be added). Please add whether the assumed alpha was one- or two sided. Procedure “The study will end for women who are not pregnant within 1 year, and in case of fetal demise after 16 weeks gestation.” Does this mean that the intervention ends for these groups of patients? Or does is mean that data collection and follow up ends there? Please specify. Does this mean that women with an early pregnancy loss <16 wks (miscarriage or termination) are eligible to continue in the study? Does it mean that women with a live birth >16 wks and early neonatal death are to continue in the study and are followed up? Lifestyle Intervention The intensity of the lifestyle intervention is unclear to me: please specify whether contact with the personal coach is likely to occur every week/ month/ bimonthly, and provide a minimum maximum total intensity estimate. Psychological guidance How are the eating disorders diagnosed: are they based on self-report or based on screening within the RCT (if so: using which tool)? Please specifiy Will psychological guidance only be made available to those with clinically manifest DSM psychiatric disease, or will a spectrum of more subtle disorders also be treated? What happens with women with depression or anxiety or phobias; are they also eligibile for treatment? Primary outcome Please make clear exactly how the primary outcome is defined: is it weight change from study inclusion to 6 wks postpartum measurement in kg? Because of the mention of OIM guidelines, it was not clear to me whether the study aims to determine % if women within recommended range according to IOM, or whether it was number of kg or percentage weight change. Please specify. There is some concern on what clinical relevance the chosen primary outcome has, which has partially been tackled. The other problem with the choice of this primary outcome, is that it requires an extra visit and is not part of routine care. This increases the likelihood of not recording the primary outcome, which may be of considerable concern. The choice of primary outcome seems to have been driven by maternal obesity and not by the smokers that I think the study also wants to target (or are only obese smokers eligible?). If all smokers regardless of BMI are eligible and make up a large proportion of those included, the chance of finding a difference in the primary outcome is negatively affected. How will the primary outcome (weight change to 6 wks postpartum) be affected by improvements in preterm birth rates by smoking cessation (ie women that have delivered preterm have lower gestational weight gain and may therefore have an

	‘advantageous’ primary outcome, even though preterm birth is not a desired outcome)? Perinatal Outcomes These need to be defined (eg what is IUGR; is it based on birthweight <p10 <p5 for gestational age or simply <2500 grams?) or does it involve ultrasound measures (as specified in the most recent published FGR definition)? Similarly: please define preterm birth, please differentiate between indicated and spontaneous preterm birth. GDM is diagnosed according to the NVOG at 7 mmol/l fasting blood glucose and 7.8 mmol/l 2 hour blood glucose (according to the WHO 1999 guidelines). However, the region in which the study will run has implemented different guidelines. Please make sure which of these GDM diagnoses will be applied in this study. Also, it is unclear to me whether the OGTT pre- and postnatal will be used to guide clinical care , and if so which cut-offs will be used to commence diabetes care? Would it be worthwhile also collecting the need for fertility care, and not just time to pregnancy? Statistical analysis plan Is not discussed: consider adding. Disclosures Smarter pregnancy M health app and Zwangerfit seem to be registered trademarks. Are these available in the study free of cost? How will these be available for pregnant women in the future, what is the involvement of the companies in the proposed study’s design/ execution/ papers, please disclose any financial or in kind contributions these companies may have made to this study.

VERSION 1 – AUTHOR RESPONSE

Reviewer # 1

We acknowledge the positive comments from the reviewer on our manuscript. We appreciate the suggestions and feedback that is given to improve the description of our study protocol.

1. Title: The title is focusing on smoking reduction while this is a secondary outcome. The reviewer suggested to make this clearer in the title.

We now shifted the focus away from the aim of the lifestyle intervention in the title onto the population the study is targeting on: “Towards Prepared mums (TOP-mums) for a healthy start, a lifestyle intervention for women with overweight and a child wish: Study protocol for a randomised controlled trial in the Netherlands”.

2. Abstract: Can it be made clearer what is meant by “health of mother and child”?

This part of the sentence has now been deleted because the change of secondary outcome parameters into exploratory outcome measurements. “Health of mother and child” has thereby become exploratory endpoints and are therefore no longer mentioned in the aim of the study in this part of the abstract (line 42).

3. We have chosen weight change from baseline to 6 weeks postpartum as primary outcome while we plan to run the trial up to 12 months postpartum. The reviewer asked if we can comment on this in the protocol.

As primary outcome measurement we have chosen weight change from baseline to 6 weeks postpartum because our primary aim is to study whether the TOP-mums lifestyle intervention will have effect on lifestyle behaviour. However, lifestyle behaviour change such as change in diet and physical activity is not one concise outcome. In addition, most lifestyle behaviour components and in particular change in diet cannot be measured in an objectively manner and are therefore at risk of bias. Thereby, weight is a not-invasive measurement which will contribute to the minimisation of missing values of the primary outcome. Therefore, we have chosen weight change as primary outcome based on the assumption that lifestyle behaviour change will result in weight change. When we will determine that the TOP-mums lifestyle intervention results in weight change, the next step is to study whether the intervention has influence on other, secondary and exploratory outcomes. We expect to find an influence of the intervention on the other, secondary outcomes because of the known relationship between weight/BMI and cardiometabolic comorbidities which makes weight change a relevant primary outcome in our opinion.

The rationale behind the follow-up up to 12 months postpartum is to create the opportunity to study whether the effort before and during pregnancy to stimulate lifestyle behaviour change results in a sustainable healthy lifestyle. When the mother has proven to be successful in sustaining a healthy lifestyle, we assume that this will have a positive effect on lifestyle that will be passed onto the next generation.
4. We are collecting many variables to be used as confounders. The reviewer's concern is, if we have only approximately 15-16 women per stratum, how we take into account type I and type II errors.
We indeed will collect many variables. However, we do not plan to take these variables into account as confounders. The variables we will collect, will be studied as secondary outcome measures or as exploratory outcomes.

In total, we will need 62 women to evaluate the primary outcome measurement with sufficient power. Randomisation will take place based on two strata: being overweight or obese, and smoking status (yes/no). Instead of performing subgroup analyses based on these stratification factors, we are planning to adjust for these stratification factors in the statistical analysis. This will lead to an increase in power and a decrease in type I error rate as has been demonstrated by extensive statistical literature (as described by Kahan & Morris, 2012, BMJ).

With regard to the power of the study to determine differences in secondary outcome measurements, we redefined most secondary outcome measurements as exploratory (as further commented on in comment 4 of reviewer #2).
5. Introduction: The reviewer suggested to put the info regarding smoking effect together in the second paragraph.
We thank the reviewer for this suggestion. We now structured the second paragraph of the introduction in that way that the information about maternal obesity is separated from the information about maternal smoking.
6. Introduction: The reviewer asked to use more recent references, in particular reference 9 and 10.
We critically revised the references and we replaced the outdated references for more recent papers.
7. Randomisation: The reviewer is wondering how we cope with only 15 women per stratum resulting in issues of power.
We commented on this question of the reviewer in comment 4.
8. How do we exclude women who are mentally disabled?
When women are known with an intellectual disability according to the DSM5 criteria, they will be excluded from the study. We now clarified on this in the manuscript on page 13.
9. Can we be clearer on the recruitment strategy? How and where are we going to reach gynaecologists, midwives, general practitioners and what is meant by youth healthcare division? Geographical region, number of healthcare providers, number of deliveries in one year in this region?

What kind of magazines and lay press is meant, how are authors going to organise this? What is the suspected number and timeframe of this type of recruitment?
We gratefully thank the reviewer for her supplementary questions regarding the recruitment strategy. We now described the recruitment strategy more precise on pages 13-14 of the manuscript.
10. The reviewer is wondering why we do target a mean difference in weight from baseline to 6 weeks postpartum.
We gratefully thank the reviewer for her critical appraisal of the primary outcome of our study. Actually, our primary outcome consists of three parts: preconception mean weight difference, mean weight difference during pregnancy and mean weight difference from birth to 6 weeks postpartum. The preconception period has not been taken into account when considering weight at 6 weeks postpartum in comparison to prepregnancy weight. In addition, we expect that differences in mean weight between intervention and control group will especially derive from the preconception and pregnancy period. When women in the intervention group lose more weight in the preconception period and gain less weight in the pregnancy period than women in the control group, a mean weight difference should be detectable at 6 weeks postpartum regardless whether they reach their prepregnancy weight or not. For practical reasons, we have chosen for the endpoint of 6 weeks postpartum. We deliberately did not choose to include a weight measurement at moment of delivery because of the different measurements instruments that need to be used in that case which might introduce measurement inaccuracies. In addition, measuring weight at delivery by midwifes or gynaecologists is not consequently integrated in clinical practice in the region of Maastricht which might introduce missing values. By determining the endpoint at 6 weeks postpartum, we can ensure that the whole pregnancy period is included in the primary outcome.

We elaborated on the reason behind the choice for weight change as primary outcome before in comment 3.
11. Procedure: The reviewer asked to be more precise on how and when potential participants will be screened for eligibility.
In line with the reviewer's recommendation (as well as with the recommendations of reviewer #2), we now expanded on the procedures that will be followed before randomisation. We agree that the sentence "The informed consent procedure enables follow-up after discontinuation of the RCT in these women" was unclear. We clarified this on page 16.
12. Care as usual: Try to be more precise what care as usual means during preconception care.
We now elaborated on care as usual per period (before, during and after pregnancy) on pages 17-18.
13. Lifestyle intervention: Can we comment on the results from our earlier qualitative study as the reviewer haven't found a reference to look into the details of these results?
The qualitative study we have performed before, is currently under consideration for publication. It is therefore not possible yet to refer to this study.
14. Who will be the personal coach? Will they be trained and if so, by whom?
The personal lifestyle coach is one of the researchers with a medical background and is trained in motivational interviewing. We now added this in the manuscript (lines 301-302).
15. Eating disorders: How are we going to diagnose this? Who will provide the psychological guidance? How do we register the adherence and compliance for this guidance?
Eating disorders will be diagnosed by a psychologist using the DSM-5 diagnostic criteria. The psychological guidance will be provided by a mental health care institution which is specialised in the treatment of obesity in combination with eating disorders. This institution will register adherence and compliance to this guidance and report this to us. We elaborated on this in the Lifestyle intervention section of the manuscript (page 20).
16. Who is going to execute the postpartum consultations to support breastfeeding including the dietary advice?
Care as usual in the Netherlands provide support in breastfeeding by maternity care in the first week postpartum. When women experience difficulties with breastfeeding, further support will be executed by a trained lactation consultant as now mentioned in lines 349-352 on page 21. Dietary advice will be

provided by a dietician, who is also trained as a lactation consultant which makes it possible to provide combination consultations.
17. Who will be the trained professional for enhancement of the physical activity?
The physical activity program in the preconception period will be offered by the sports department of the municipality of Maastricht. The professionals employed in the sports department are trained in physical education (lines 356-357).
18. Will the paediatric physiotherapist be a member of the research team? Where will he/she be working regarding accessibility for the mothers/babies?
The paediatric physiotherapist will visit the participating mothers and children at home in order to stimulate playing with their child, emotional bonding, and stimulating motor development in the safety of their own home. Accessibility will therefore no threshold in this early postpartum phase. The paediatric physiotherapist is hereby able to discuss which kind of activities mothers wishes to catch up after childbirth in addition to the individual consultations. For example, it is possible to participate in swimming classes which are targeted on swimming with their baby or baby mindfulness classes.
19. Do mothers receive incentives for all these efforts?
Indeed, mothers receive a reward in before, during and after pregnancy to acknowledge them for participating in our study. The reward will match with the life phase in which women will receive this, such as a 3D ultrasound during pregnancy. We added a paragraph Incentives in the manuscript (lines 562-565, page 34).
20. Is the lifestyle coach trained in motivational interviewing to support women to quit smoking?
The personal lifestyle coach is indeed trained in motivational interviewing. This has been clarified in lines 301-302, pages 18-19 of the manuscript.
21. Where will study visits take place?
The study visits will take place at Maastricht University Medical Centre+. This is added in line 383.
22. Why do you calculate gestational weight gain up to 36 weeks and not at the last prenatal consult or at delivery?
This is a good point made by the reviewer. According to the definition of gestational weight gain mentioned in the most recent guidelines from the Institute of Medicine (the amount of weight a pregnant woman gains between the time of conception and the onset of labour), it would be more appropriate to calculate gestational weight gain up to the last prenatal study visit. This has now been changed in the manuscript (lines 412-413). We deliberately did not choose to include a weight measurement at delivery because of reasons mentioned in response op comment 10.
23. Can we comment on the use of double labelled water technique to measure BMI? How are we going to organise this in pregnant and postpartum women?
Using the technique with deuterium labelled water, we aim to measure the fat and fat-free mass of the participating women in addition to BMI. Body composition provides further information by describing the relative contribution of each compartment to total body weight. It is assumed that fat-free mass contains all body water. During pregnancy, the high-water content of gestational specific fat-free mass means that water tracers readily escape into the gestational tissues. This leaves a low concentration in the compartment from which it is measured. The assumption that all lean tissue has the same water concentration would lead to overestimation of lean body mass and underestimation of fat in pregnant women. There are adjustments available for expected gestational water gain for different gestational ages which we will apply to the calculations. Deuterium oxide is not toxic, neither for the women nor for the foetus. In the postpartum period (body composition will be measured 6 months postpartum) it is assumed that tissues are re-established to the preconception situation. The adjustment for the calculations of fat and fat-free mass are now mentioned in the manuscript (lines 420-425).
24. Which guidelines will be used to determine gestational diabetes, hypertension and other perinatal outcomes? Are they the same in each site?
The guidelines that will be used to determine GDM, GH, preeclampsia and other perinatal outcomes are the guidelines from the Dutch Society of Obstetrics and Gynaecology. We clarified the cut-off points that are used within these guidelines and references are added of these guidelines (page 31).

25. Please specify the rationale to measure pulse wave velocity and retinal vascular images related to preconception health and impact in next generations?
Although cardiovascular morbidity such as a high blood pressure might not (yet) be present in women participating in the study, a precursor might already be present and might play a role in the transmission of health risk to the next generation. Since arterial stiffness and retinal microvasculature are both established as prognostic parameters for cardiometabolic morbidity and are therefore included in this study. This is now added to the manuscript on lines 460-465.
26. Sample collection: The reviewer missed the rationale behind as well as a clear pathway about the how and why we collect microbial flora, placental tissue and breast milk.
We regret that we have not made clear why we would like to collect the mentioned samples. On pages 32-33 of the manuscript, we now added the rationale behind the collection of microbial flora, placental tissue and breast milk composition.
27. Legend for Figure 1: The sentence “The effects of lifestyle improvements in this episode can impact health of the entire life span” sounds a bit contradictory to the listed possible impact behind it as these are formulated in a negative way.
This is a good point made by the reviewer. We adapted the sentence now.

Reviewer # 2
We would like to thank the reviewer for her positive comments on the importance of our study. We appreciate the suggestions and feedback that is given to improve the description of the methods.
1. Please add the paper by Lan et al. 2017 to the references.
This paper has now been added to the references and is mentioned in line 626 on page 38.
2. Please pay more attention to the small sample size and possible opposing effects of the intervention aimed at smokers and at obese women.
The small sample size is now mentioned in the Strength and Limitations section as is also mentioned before in comment 4 of the editorial requests.
3. The text could benefit from English language editing.
We added a co-author to the list of authors (Dorien Reijnders). She is involved in the execution of the TOP-mums study and has extensive research experience in the USA. She critically revised the manuscript and edited on English language.
4. Abstract: The reviewer suggested to include only realistically achievable goals in the aim of the study.
We agree with the reviewer that it will not be achievable to determine the effect of all secondary outcome measurements with the current sample size of the study. Therefore, we decided to redefine the outcome measurements cardiometabolic parameters, time to pregnancy, need for fertility treatment, perinatal complications of mother and child, and lung function of the child as exploratory outcomes instead of secondary outcome measures.
5. Abstract: Mentioning the intended sample size would benefit the abstract.
The sample size is now mentioned in the abstract.
6. Strength and Limitations: Add small sample size to the limitations.
The small sample size is now mentioned in the Strength and Limitations section.
7. Introduction: Please rephrase lines 48-52 to better reflect the differential effects of maternal smoking and maternal overweight/obesity.
These lines are adjusted, according to the suggestion of the reviewer (pages 7-8).
8. Figure 1: Please mention pregnancy loss in the figure.
Miscarriage is now mentioned in Figure 1.
9. Please be consistent in the use of the name of the study.
The name of the study has now been changed in Figure 1. A search for inconsistent use of the name of the study did not result in other inconsistencies in the manuscript.
10. Please rephrase line 55 as LGA is not an example of reduced foetal wellbeing.
This sentence is rephrased accordingly.
11. Study design: Please add minimum and maximum block sizes.

We now added the possible block sizes (line 177).
12. Setting and study population: The inclusion criteria mention nothing about smoking, which is inconsistent with the introduction and abstract.
It is correct that nothing is mentioned about smoking in the inclusion criteria. Women need to have a BMI ≥25 kg/m2, and plan to conceive within one year and aged between 18-40 years. However, it is not necessarily that they smoke to be included in the study. The reason that smoking is mentioned in the introduction, is that when women are eligible for participation in the study and they smoke, we will pay attention to smoking cessation in the lifestyle intervention.
13. Are any language restrictions applied to the inclusion criteria?
Only women who speak and read Dutch and/or English will be included in the study. This is now mentioned in lines 198-199 in the manuscript.
14. Are any limitations applied in terms of women's eligibility if their pregnancy test is already positive when they first present for randomisation?
When women first present for randomisation and their pregnancy test is positive, they cannot participate in the study. This is now added to the manuscript in line 200.
15. Are there any limitations applied to the population (e.g. are women in fertility clinics eligible)? What repercussion does participation have on their treatment at the fertility clinic?
No limitation will be applied to the population. We now mentioned this in the manuscript (line 199 and 274-277).
16. Are women eligible for the study in subsequent pregnancies? E.g. after a miscarriage or term birth, can they be randomised again?
We also elaborate on this question in our answer on comment 21 of reviewer #2. We have now clarified the procedure after a miscarriage in manuscript (page 12).
17. Recruitment: Are potential study participants to complete give their informed consent in writing?
Women who approved to participate in the study, will give their informed consent in writing. We now made this clear in the Procedure section of the manuscript. Furthermore, we added the English translation of the Informed Consent form as supplementary file.
18. Sample size: None of the studies quoted in this section report on postpartum weight differences.
We thank the reviewer for her critical appraisal of the sample size calculation. Studies are available for preconception mean weight difference, and mean weight difference during pregnancy which we used to justify the mean difference in weight we expect to find. For the mean weight difference from birth to 6 weeks postpartum, we could not find any studies that report on relevant outcome measurements for our primary outcome.
19. Sample size: Please specify on the drop-out rate, in particular break down the percentages used to determine the drop-out rate.
The drop-out rate can be broken down in three categories: foetal demise >16 weeks of gestational age, women not being pregnant within one year after randomisation, and discontinuation of participation in the study. Based on previous studies, foetal demise after 16 weeks of gestational age occurs around 1% of pregnancies (Simpson 1990; Zhou 2016). The reviewer mentioned a percentage of 15-20%, which we assume is based on the total number of miscarriages. However, in the TOP-mums study only women with a miscarriage >16 weeks of gestational age will drop-out. Time to pregnancy longer than one year was earlier showed to be approximately 21% in women with overweight or obesity (Hassan 2004; Ramlau-Hansen 2007). Based on earlier studies, we expect a drop-out rate due to discontinuation of the study of around 22% (Vinter 2011; Althuizen 2013; Mutsaerts 2016). In total, this result in drop-out rate of 44%. These numbers are now added to the Sample size section of the manuscript (lines 245-246).
20. Sample size: Please add whether the assumed alpha was one- or two sided.
The alpha was two-sided and is now mentioned in line 243.
21. Procedure: "The study will end for women who are not pregnant within 1 year, and in case of foetal demise after 16 weeks of gestation". Does this mean that the intervention ends for these group of participants? Or does it mean that data collection and follow-up end there? Does this mean that women with an early pregnancy loss <16 weeks of gestation are eligible to continue in the study?

Does it mean that women with a live birth >16 weeks and early neonatal death are to continue in the study and are followed up?
These are pertinent remarks from the reviewer. Both the intervention and follow-up will end for women who are not pregnant within one year after randomisation, and in case of foetal demise after 16 weeks of gestation. We clarified foetal demise >16 weeks of gestational age as foetal demise between 16-24 weeks of gestational age, since a live birth >24 weeks will be considered as preterm birth. Women with a live birth >24 weeks of gestational age and early neonatal death may continue the study and follow-up until one year postpartum. Indeed, women with an early pregnancy loss <16 weeks of gestational age are eligible to continue the study for follow up of a potential second pregnancy. We clarified this in de Procedure section of the manuscript (page 12).
22. Lifestyle intervention: The reviewer mentioned that the intensity of the lifestyle intervention is unclear, please specify on this.
We now added a guideline for frequency of contacts with the personal coach and dietician as Supplementary file 4 to give more insight in the intensity of the lifestyle intervention. We also provided more information about the intensity in the text of the manuscript (lines 299-301 and 350-352).
23. Psychological guidance: How are eating disorders diagnosed?
Eating disorders are diagnosed by a psychologist using the DSM-5 diagnostic criteria. We now mentioned this in the Lifestyle intervention section on page 20.
24. Will psychological guidance only be made available to those with clinically manifest DSM psychiatric disease, or will a spectrum of more subtle disorders also be treated?
Indeed, psychological guidance will only be made available to the women with an eating disorder as diagnosed using the DSM-5 diagnostic criteria. Once they will be psychologically guided because they are diagnosed with an eating disorder, there will also be attention for more subtle disorders in the treatment. We clarified this in the paragraph “Psychological guidance”.
25. Primary outcome: Please make clear exactly how the primary outcome is defined.
The primary outcome measurement is defined as weight change in kg. This is clarified in the manuscript (lines 50, 235, 413 and 415).
26. The reviewer had some concern on what clinical relevance the chosen primary outcome has, which has partially been tackled. In addition, the primary outcome requires an extra visit and is not part of routine care. This increases the likelihood of not recording the primary outcome, which may be of considerable concern.
We previously commented on our rationale behind the choice for the primary outcome in comments 3 and 10 of reviewer #1. In light of the concern of the reviewer that the primary outcome requires an extra visit, an important reason to choose for weight as primary outcome is a non-invasive and quick measurement and thereby minimise the risk of missing values of the primary outcome. Furthermore, measuring weight is also possible by visiting the mother at home which will enhance the possibility of collecting primary outcome measurements.
27. The reviewer is wondering whether all smokers – regardless of BMI – are eligible for the study. In that case, the chance of finding a difference in the primary outcome is negatively affected.
Only women with a BMI ≥25 kg/m2 are eligible for study participation, regardless of smoking status. The primary outcome will therefore not be affected by participants with a BMI <25 kg/m2 who are not eligible to participate in the study. We regret this was not clear and we now clarified this in the manuscript (lines 197-198).
28. How will the primary outcome be affected by improvements in preterm birth rates by smoking cessation?
We do not expect a large effect of the moment of delivery on weight at 6 weeks postpartum. One of the reasons to choose the primary endpoint at 6 weeks postpartum and not for example at delivery or at the last prenatal visit, was that differences in weight change are expected to be much larger compared to weight changes at 6 weeks postpartum. Hence, we suspect that the influence of preterm birth on the primary endpoint is as small as possible.
29. Perinatal outcomes: These need to be further defined.
The perinatal outcomes are now further defined in on page 31.

30. The reviewer mentioned that it is unclear to her whether the OGTT pre- and postnatal will be used to guide clinical care. And if so, which cut-offs will be used to commence diabetes care?
The measurements performed within the context of this study and are not part of usual clinical practice can result in incidental aberrant findings. In case of such aberrant findings, these will be reported to the general practitioner, midwife and/or gynaecologist of the women. Subsequently, they will be responsible for follow-up and treatment of this aberration.
31. Would it be worthwhile to also collect the need for fertility care, and not just time to pregnancy?
This is a very good point made by the reviewer. It is indeed worthwhile to also collect the need for fertility care, which we now included in the study protocol (lines 490-492).
32. Consider adding a statistical analysis plan. In such a section, we can elaborate on whether we have planned to exclude those who fail to follow the lifestyle program from intention to treat analysis.
In the first version of the manuscript, we included a paragraph “Data analysis”. We now changed the heading of this paragraph into “Statistical analysis plan”.
33. Disclosures: Smarter Pregnancy M health app and Zwangerfit seem to be registered trademarks. Are these available in the study free of cost? How will these be available for pregnant women in the future? What is the involvement of the companies in the proposed study’s design/execution/papers? Please disclose any financial or in-kind contributions these companies may have made to this study.
Both the Smarter Pregnancy M health app and Zwangerfit® are available free of cost during the study. For Smarter Pregnancy, we bought a license from Slimmere Zorg BV to receive the right to use the M health app in the TOP-mums study. From 2016 to April 2019, Régine P.M. Steegers-Theunissen was CSO of Slimmere Zorg BV. Régine P.M. Steegers-Theunissen is involved in the study and has an advisory role. The Smarter Pregnancy M health app is already covered by health insurance companies which will ensure the free of cost availability in the future. Zwangerfit® is a company which offers physiotherapists courses to train them to become eligible to perform Zwangerfit® classes. We paid for this course to train a physiotherapist in Zwangerfit®. Zwangerfit ® is not involved in the study. We received a grant to be able to offer the Zwangerfit® classes for the study participants free of costs. After the study has been finished, Zwangerfit® might be offered in exchange for a small contribution of participants.

We are pleased to resubmit our manuscript for consideration by BMJ Open.

VERSION 2 – REVIEW

REVIEWER	Annick Bogaerts KU Leuven University of Antwerp Belgium this reviewer is project manager of the Inter-Act study, a randomised controlled eHealth supported interpregnancy lifestyle intervention, https://www.ncbi.nlm.nih.gov/pubmed/28549455
REVIEW RETURNED	01-Sep-2019

GENERAL COMMENTS	authors have made sufficient and clear adaptations according to my comments, thank you

REVIEWER	Rebecca Painter Amsterdam University Medical Centres, location AMC I may be collaborating with the authors on a new preconception intervention study- present stage of collaboration is discussion about possible future collaborative grant proposal. The collaboration does not hinge on publication of the present submission.

REVIEW RETURNED	01-Sep-2019

GENERAL COMMENTS	Most of my questions on the first draft version have been answered satisfactorily by the authors. However, a number of issues remain: Abstract still states in the opening line that smoking leads to LGA and preeclampsia, when the opposite is true. Please change the phrasing: I would prefer if the reference to smoking and its effects on pregnancy outcomes were omitted here, as it leads to confusion. The loss- to-follow-up question is not entirely clearly answered. It is now clear that women with a pregnancy loss or termination <16 wk are eligible to continue the intervention and the follow up. But until when they can participate needs further specification: is this until 12 months after initial randomisation, or until 12 months after their pregnancy loss or termination? Please specify in the text of the paper. The English could be further improved. Although the language is generally clear, there are some unnecessary mistakes in the present version. Examples include the use of the plural of advice= advice (not advices); plural of midwife= midwives (not midwifes); the plural of RCT would be RCTs (not RCT's). Also regarding the use of the infinitive, e.g. "women interested to participate" should be rephrased as "women interested in participating". Could the authors have a native English speaker review their manuscript? Data collection: Could the authors be clearer about the source from which they will derive the pregnancy outcomes? Will these be self-reported? Or will they be extracted from the hospital or midwife dossiers? Or from the Perined registry? The conflict of interest statement: I thank the authors for altering this section. One of the authors was a recent CEO for a company that sells one of the products used in the intervention. This is now correctly declared. However, whether the author has any present commercial dealing with the company (eg shares or income) should be also declared.

VERSION 2 – AUTHOR RESPONSE

Reviewer # 1

We gratefully thank the reviewer for her recommendation to publish our manuscript.

Reviewer # 2

We would like to thank the reviewer for her positive comments on the revision of our manuscript. We appreciate her suggestions to further improve the manuscript.

1. Please change the opening line of the abstract.

We now omitted the reference to smoking and its effects on pregnancy outcomes in the abstract.

2. For the reviewer it is not entirely clear until when women with a pregnancy loss or termination <16 weeks of gestational age can participate in the study.

This is a good point made by the reviewer. We now added a sentence to make clear that women with a pregnancy loss or termination <16 weeks of gestational age can participate until 12 months after initial randomisation (page 10).

3. The text could benefit from English language editing.

We further edited the English language as highlighted with 'tracked changes' in the manuscript.

4. Data collection: Could we be clearer about the source from which we will derive the pregnancy outcomes?

We now added a sentence about the source from which we will derive the pregnancy outcomes (page 30).

5. The conflict of interest statement: It should be declared whether the author has any present commercial dealing with the company.

In the period between the last submission of the manuscript and the current submission, the situation of the property of Smarter Pregnancy has been changed. Currently, Smarter Pregnancy is property of Erasmus MC, Rotterdam. This has now been changed in the conflict of interest statement.

We are pleased to resubmit our manuscript for publication by BMJ Open.