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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

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ABSTRACT

Introduction: Periconceptional obesity and smoking are associated with a higher risk of adverse perinatal outcomes such as gestational diabetes mellitus (GDM), preeclampsia, large for gestational age (LGA), operative delivery and preterm birth. Lifestyle interventions during pregnancy have resulted in insufficient effects on reducing these perinatal complications. A few reasons for this disappointing effect can be suggested: 1) the time period during pregnancy for improvement of developmental circumstances is too short; 2) the periconception period in which complications originate is not included; and 3) lifestyle interventions might have been not multidisciplinary and customised enough. A preconceptional lifestyle intervention is potentially more sufficient in reducing perinatal complications. Therefore, the aim of the TOP-mums study is to evaluate the effect of a preconceptionally started lifestyle intervention on weight change and the health of mother and child.

Methods and analysis: This protocol outlines a non-blinded, randomised controlled trial. Women (18-40 years of age) with a pregnancy wish within one year, with overweight or obesity (Body Mass Index (BMI) ≥ 25.0 kg/m^2) will be randomised to either the intervention or control group. The intervention group will receive a multidisciplinary, customised lifestyle intervention stimulating physical activity, a healthy diet and, if applicable, smoking cessation. The control group will receive care as usual. The lifestyle intervention and monitoring will take place until

12 months postpartum. The primary outcome is difference in weight from baseline to 6 weeks postpartum. Secondary outcomes are gestational weight gain, postpartum weight retention, smoking cessation, cardiometabolic alterations, body composition, dietary and physical activity habits, time to pregnancy, perinatal complications of mother and child, and lung function of the child. Vaginal and oral swabs, samples of faeces, breast milk, placenta and cord blood will be stored for evaluation of microbial flora, epigenetic markers and breast milk composition. Furthermore, a cost-effectiveness analysis will take place.

Ethics and dissemination: Ethical approval was obtained from the medical ethics committee of Maastricht University Medical Centre+ (NL52452.068.15/METC152026).

Trial registration number: ClinicalTrials.gov NCT02703753.

Keywords: Lifestyle, preconception, non-communicable diseases, pregnancy complications

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This randomised controlled trial is innovative by evaluating effects of a lifestyle intervention that starts preconceptionally and continues until one year postpartum;
- The strength of the intervention is that it is multidisciplinary and personalised, taken into account the wishes, needs and opportunities of the women at risk;
- This study will collect a broad range of data, including longitudinal data regarding mechanisms hypothesised to be involved in the intergenerational transmission of diseases, which is scarcely studied yet and allows the generation of new hypotheses;
- Women who are willing to participate in the study are potentially more motivated to change their lifestyle, also when allocated to the control group;
- We anticipate on the frequently occurring dropout in previous lifestyle interventions, by closely involving the target group in all stages of the lifestyle intervention (from developing the study design to dissemination of the results) and the tailored approach of the intervention.

INTRODUCTION

Worldwide, the prevalence rates of chronic diseases such as cardiovascular diseases, dyslipidaemia and diabetes mellitus are increasing. The rising burden from these chronic diseases imposes new challenges for health care.[1] Key risk factors in the development of chronic diseases are lifestyle habits such as smoking, a lack of physical activity, an unhealthy diet and overweight. As illustrated in Figure 1, there is increasing evidence suggesting that the influence of exposure to a certain lifestyle originates in the periconceptional period.[2-5] By tackling its earliest origins, improving lifestyle preconceptionally has the potential to benefit global public health by addressing the increasing problem of chronic diseases.

Obesity and smoking before, during and after pregnancy are the origin of short term adverse pregnancy and birth outcomes,[5] and of chronic diseases for mother and child in the long run. Regarding the short term consequences, unhealthy lifestyle of women of reproductive age is associated with an increased time to conceive.[6-8] During pregnancy, these women are at risk to develop complications as gestational hypertension (GH), preeclampsia, gestational diabetes mellitus (GDM) and operative delivery.[9-11] Moreover, maternal obesity has harmful effects on foetal wellbeing, such as a higher risk of congenital abnormalities, large for gestational age (LGA), and birth trauma as consequence of shoulder dystocia.[12 13] Intra-uterine exposure to

smoking is associated with a higher risk on small for gestational age (SGA) and preterm birth.[14] Besides, neonates of these women are more likely to be admitted to the neonatal intensive care unit.[15]

The risk of adverse events among offspring can extend through adulthood, demonstrating a vicious circle of intergenerational transmission of diseases.[3 4 16] Several studies suggest that intra-uterine exposure of a certain lifestyle can increase the risk of cardiovascular, metabolic and endocrine disease in adult life by unfavourable foetal programming.[2 4] Studies with animal models indicate that epigenetic processes are an important link between maternal lifestyle habits, and the risk of obesity and chronic diseases in adult offspring. Epigenetic processes modulate gene transcription, establishing an epigenome during embryogenesis and early development of the foetus.[17] Furthermore, recent research suggests microbiota as underlying mechanism for intergenerational transmission of obesity.[18] Bacterial diversity is influenced by obesity and gestational weight gain.[19] It is hypothesised that the transfer of obesogenic microbial flora from mother to child during birth contributes to the intergenerational transmission of diseases.[20]

In an attempt to prevent perinatal complications, previous studies addressed lifestyle in women with an intervention during pregnancy. Although these interventions were successful in limiting gestational weight gain, they were not successful in reducing GDM, preeclampsia and LGA in women with obesity.[21] Several reasons can be hypothesised to clarify this disappointing effect: the pregnancy period is too short to achieve sufficient impact on pregnancy outcomes, these lifestyle interventions did not include the periconception period in which perinatal complications originate, and previous developed lifestyle interventions could be improved with a more multidisciplinary and customised approach. Improving lifestyle preconceptionally might overcome these issues. Indeed, data from large population-based studies have shown that BMI change between pregnancies from overweight or obesity before the first pregnancy to normal weight before the subsequent pregnancy decreased the risk of GDM and LGA.[22 23] A preconceptionally started lifestyle intervention can lead to weight reduction, which in turn is hypothesised to result in positive changes in epigenetic and microbiota markers. This might prevent the development of periconceptional and consequently perinatal complications and a transmissible harmful epigenetic predisposition in the offspring. Finally, the intergenerational transmission of diseases might be disrupted and the current epidemic of chronic diseases might be reduced.[2 24 25]

Aim

The primary aim of this study is to evaluate the impact of a preconceptionally started lifestyle intervention on weight change in women with overweight or obesity and with a child wish. Secondary study aims are to evaluate the effect of the lifestyle intervention on gestational weight gain, postpartum weight retention, smoking cessation, cardiometabolic alterations, body composition, lifestyle habits, time to pregnancy, and perinatal complications such as GDM, GH and preeclampsia in the mother, and perinatal complications such as SGA, LGA and preterm birth, cardiometabolic alterations, and lung function in the child. Furthermore, changes in the microbial flora, epigenetics and breast milk composition will be evaluated. Finally, a cost-effectiveness analysis of the lifestyle intervention will be conducted.

METHODS AND ANALYSIS

This protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement (see Supplement 1: SPIRIT checklist).[26] The TOP-mums study was ethically approved by the medical ethics committee of the Maastricht University Medical Centre+ (MUMC+; NL52452.068.15/METC152026).

Study design

This study is a randomised controlled trial (RCT) in which the participants and investigators will not be blinded due to pragmatic reasons. Participants will be randomised 1:1 in either the intervention or control group using block randomisation, with random block sizes. Randomisation will be stratified for overweight (BMI 25.0-29.9 kg/m^2), obesity (BMI ≥ 30.0 kg/m^2), and smoking status.

Setting and study population

The study will be conducted in the South of Limburg, the Netherlands and is initiated and coordinated by MUMC+. Women will be eligible to participate in this study when meeting the following criteria: a wish to become pregnant within one year, 18-40 years of age, and having a BMI ≥ 25.0 kg/m². Women will be excluded in case of having a haemodynamically significant heart disease, restrictive lung disease, congenital metabolic disease, being mentally disabled, bariatric surgery in the past, and having diabetes type II dependent on medication.

Recruitment

Multiple recruitment strategies will be used to reach an adequate number of potential participants (see sample size). First, gynaecologists, midwifes, general practitioners, and the

Youth Healthcare Division will inform potential participants. Second, advertisements will be placed in regional magazines, lay press and on social media. Third, in order to conduct another – cross-sectional – study, a questionnaire was sent to women of reproductive age in the region. Simultaneously, women were asked if they appreciated to be approached for the current study. Women who fulfil the inclusion criteria and who gave consent, will be contacted for participation. Before participation, women will be asked for informed consent based on the provided information.

Sample size

A sample size calculation is conducted for the primary outcome measure, defined as the mean difference in body weight from baseline to 6 weeks postpartum. In a previous study that evaluated the effect of a lifestyle intervention in subfertile women, a mean reduction of 3.4 kg resulted in a higher natural conception rate.[27] Further, a weight reduction of 5-10% was associated with a reduction of the incidence of type 2 diabetes in adults at risk due to a BMI ≥ 24.0 kg/m².[28] During pregnancy, lifestyle interventions resulted in a 1.5 kg reduction in gestational weight gain.[29] In some studies, this weight reduction was associated with a lower prevalence of preeclampsia.[29] Taken these previous results into account, our research group determined a mean difference of 5 kg with a SD of 7 kg between the study groups as clinically

relevant. For the sample size calculation, an alpha of 0.05 and a power of 80% is used. Taken into account a drop-out rate of 44% (based on drop-out rates of other lifestyle interventions,[30-33] foetal demise after 16 weeks of gestation,[34] and time to pregnancy > 12 months[6 35 36]), a total of approximately 110 women should start the study to be able to detect a mean difference of 5 ± 7 kg with 62 women required for analysis.

Procedure

Potential participants will be screened for eligibility and after informed consent is signed, the baseline measurement will take place. Thereafter, randomisation by the software program ALEA (ALEA Clinical B.V., Abcoude, the Netherlands) will be performed allocating participants either in the intervention or control group. The study will start preconceptionally and will continue during pregnancy, until one year after delivery. The study will end for women who are not pregnant within one year after inclusion and in case of a foetal demise after 16 weeks of gestational age. The informed consent procedure enables follow-up after discontinuation of the RCT in these women. A flow chart of these procedures is presented in Figure 2.

Care as usual

Both study groups will receive care as usual. Additional to usual care, women in the intervention group will receive the lifestyle intervention as described below. In the Netherlands, usual care for women and children before, during and after pregnancy includes access to the general practitioner, pregnancy care by midwifes and/or gynaecologists, and consultations at the nurses of the Youth Healthcare Division after pregnancy. Lifestyle advices by health care professionals (according to the national guidelines) as well as referral to lifestyle guidance when indicated could take place during care as usual, which will be registered.

Lifestyle intervention

The TOP-mums lifestyle intervention is multidisciplinary and stimulates physical activity and a healthy diet, and, if applicable, smoking cessation. A qualitative study to determine the needs and wishes of the women in the target population was executed by our research group. Results are incorporated in the intervention. Each woman will be assigned to her own personal lifestyle coach, who will coordinate and guide the woman through her personal program. Women will not receive a fixed schedule, but their program will be determined based on their wishes, needs and opportunities using motivational interviewing by the personal coach.[37 38] This involves three steps: 1) lifestyle habits will be assessed by a nutrition diary, questionnaires and an activity tracker at the start of the lifestyle intervention. Based on this assessment, potential

improvements in lifestyle habits will be determined; 2) together with the woman, it will be determined which lifestyle improvement should be tackled first and goals will be formulated; 3) it will be discussed with the woman which (combination) of supporting programs, as elaborated below, will be valuable in achieving her goals and will best suit within her daily life. The program will cover the periods before, during and after pregnancy. Each phase will be accompanied by specific lifestyle advices. This lifestyle intervention is innovative by the adaptive and proactive approach and the structured offer of lifestyle guidance. In this manner, women are supported with easily accessible lifestyle guidance.

Smarter pregnancy

Each woman will be provided with a subscription to the mHealth program Smarter Pregnancy (Slimmere Zorg B.V., Bussum, the Netherlands). This coaching program supplies personal coaching of 26 weeks, based on current personal circumstances, pregnancy status, nutrition and lifestyle. It was demonstrated to improve nutrition and other lifestyle behaviours.[39-42] The tailored coaching includes a maximum of three digital posts per week, containing advices, seasonal recipes for healthy meals and additional questions addressing lifestyle behaviour, taking into account pregnancy status.

Psychological guidance

For women who suffer from eating disorders in combination with overweight or obesity, psychological support can help with sustainable improvement of lifestyle. The cornerstone of the guidance is the treatment of the eating disorder and possible other psychological comorbidities (e.g. depression). Moreover, sustainable change of lifestyle, and improvement of social and labour participation will be targeted. Cognitive behaviour therapy, cue exposure and system therapy are techniques that will be used. In general, this involves coaching sessions two to three times a week, for four months.

Dietary guidance

Individualised sessions will take place with a dietician approximately every one or two months, providing advices to improve the intake of dairy products, fruit and vegetables, while decreasing the intake of high-energy foods with little nutritional value. Diet advices are according to the recommendations of the Netherlands Nutrition Centre Foundation[43] and the intervention will target a healthy diet, without extreme regimens. During pregnancy, a target will be set for a maximum gestational weight gain, aiming at staying within the Institute of Medicine guidelines.[44] In the postpartum period, breastfeeding will be encouraged and consultations will be directed towards dietary advices for mother and child.

Physical activity

To support weekly physical activity at moderate intensity, a physical activity program conducted by trained professionals will be offered. In the preconceptional period, the physical activity program will focus on improving aerobic capacity, muscle strengthening and increasing energy expenditure. The activities will be diverse to make it attractive for the women. Furthermore, the activities will take place on different time slots and different locations in order to make it as easy as possible to join one of the activities. During pregnancy, sessions will be conducted by a ZwangerFit® trained physiotherapist. ZwangerFit® is a course that focuses on physical fitness, muscle strengthening, coordination and stabilisation, especially for the pelvic muscles. It is previously shown that these exercises reduce the risk of low back pain, and sick leave because of lumbopelvic pain during pregnancy.[45] At 6 weeks postpartum, group sessions will catch up again until 9 months postpartum, by a paediatric physiotherapist, focussing on the mother having fun in playing with their child, emotional bonding, and stimulating motor development.

Smoking cessation

To target smoking cessation, the lifestyle coach will apply motivational interviewing techniques to support women to quit smoking. If necessary, women can be referred to a smoking cessation coach for more extensive guidance.

Outcomes

Anthropometric, cardiometabolic, lifestyle habits, perinatal and postpartum outcomes will be measured and registered, and samples collected to determine the effects of the lifestyle intervention on health of the women and child (see Table 1 for an overview).

Table 1: Overview of the measurements at different time points during the study

		Preconception						Pregnancy								Postpartum				
	Baseline	*1 month*	*2 months*	*3 months*	*6 months*	*9 months*	*12 months*	*6 weeks*	*12 weeks*	*20 weeks*	*26 weeks*	*32 weeks*	*36 weeks*	*40 weeks*	*Birth*	*6 weeks*	*3 months*	*6 months*	*9 months*	*12 months*
Anthropometric measurements																				
Weight, BMI, waist and hip circumference mother	x	x	x	x	x	x	x	x	x	x		x	x	x		x	x	x	x	x
Body composition mother	x											x						x		
Weight, height and BMI child																x	x	x	x	x
Cardiometabolic outcomes																				
Blood pressure mother	x	x	x	x	x	x	x	x	x	x		x	x	x		x	x	x	x	x
Pulse wave velocity mother	x			x	x		x	x		x		x						x		x
Retinal image mother	x			x	x		x	x		x		x						x		x
Glucose, insulin levels, lipid profile, liver enzymes mother				x				x		x		x					x	x		x
OGTT mother	x										x									x

Glucose, insulin levels, lipid profile child (cord blood)														x					
Glucose, insulin, lipid profile child																			x
Lifestyle habits																			
Accelerometer mother	x			x			x	x				x					x		x
Baecke questionnaire mother	x			x			x	x				x					x		x
Nutrition diary mother	x			x			x	x				x					x		x
Three Factor Eating Questionnaire mother	x			x			x	x				x					x		x
Vitamin D mother	x											x							
Smoking behaviour questionnaire mother	x	x	x	x	x	x	x	x	x	x		x	x	x		x	x	x	x	x
CO measurement mother	x	x	x	x	x	x	x	x	x	x		x	x	x		x	x	x	x	x
Urine cotinin mother	x			x				x		x		x				x				x
Feeding pattern child																x	x	x	x	x
Perinatal outcomes																			
Time to pregnancy								x											
Miscarriage										x									
Pregnancy complications (GDM, GH, preeclampsia, IUGR)												x	x	x					
Method of delivery															x				
Induction of labour															x				
Postpartum measurements																			
Birth weight															x				
Gestational age															x				
APGAR-score															x				
Stillbirth															x				
Sample collection																			
Microbiome sampling mother	x			x	x	x	x	x		x		x					x	x	x	x
Epigenetic sampling															x					
Breast milk sampling																x				
Microbiome sampling child																x				x
Cost-effectiveness analysis																			
Cost questionnaire	x			x	x	x	x	x		x		x					x	x	x	x
EQ-5D-5L	x			x	x	x	x	x		x		x					x	x	x	x

When women become pregnant at a certain time point without completion of all preconception measurements, the remaining preconception measurements will be cancelled. Women will continue the measurements belonging to the pregnancy period. The same procedure will take place when women give birth before 40 weeks of gestational age. Abbreviations: BMI, body mass index; CO, carbon monoxide; EQ-5D-5L, Quality of life measurement; GDM, gestational diabetes mellitus; GH, gestational hypertension; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test.

Anthropometric measurements

Body weight of the women will be assessed in underwear with no shoes in kilogram to the nearest 0.1 kilograms using a medical calibrated weight scale (Model 799, seca gmbh & co. kg., Chino, USA), at each study visit. Height will be determined by a stadiometer (Model 220, seca gmbh & co. kg., Chino, USA) calibrated in 0.1 cm intervals. BMI will be calculated as the weight in kilograms divided by height in meters squared. Gestational weight gain is defined as weight from 6 to 36 weeks of gestational age and will be compared to the Institute of Medicine guidelines.[44] Postpartum weight retention is defined as the difference in weight between 6 weeks of gestational age and 6 months postpartum.

The waist and hip circumference will be measured with a non-elastic tape at the end of a natural breath at midpoint between the top of the iliac crest and the lower margin of the last palpable rib respectively on the widest point of the hip, standing on both feet equally with arms hanging down. The waist/hip ratio will be calculated. Furthermore, the body composition will

be measured at three time points during the study using the double labelled water technique with water labelled with deuterium according to the Maastricht protocol.[46]

Cardiometabolic outcomes

Fasting blood samples will be taken at different time points before, during and after pregnancy to determine blood glucose and insulin levels, lipid profile and liver enzymes. Fasting plasma glucose will be determined using the Cobas 8000 modular analyser (F. Hoffmann-La Roche Ltd., Basel, Swiss) and serum insulin concentrations using the Immulite-1000 (Siemens Healthcare Diagnostics, Erlangen, Germany). Based on this, the homeostatic model assessment of insulin resistance (HOMA-IR) will be calculated according to fasting glucose (mmol/L)*(fasting insulin (μU/L)/22.5).[47] All participants will have a 75 gram oral glucose tolerance test at baseline, 26 weeks of gestational age, and 12 months postpartum. Blood glucose and insulin concentrations will be measured after 1 and 2 hours. Fasting serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, serum alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) concentrations, will be determined using the Cobas 8000 modular analyser.

Cardiovascular alterations will be measured by systolic and diastolic blood pressure (SBP and DBP), using a validated automatic device (A&D Medical UA-789XL, Saitama, Japan) on the left arm after 5-10 minutes rest in a sitting position for four times, with one minute rest in between. Mean SBP and DBP of the three last measurements will be calculated. In addition, arterial stiffness will be assessed by the carotid-femoral and carotid-radial pulse wave velocity and Augmentation Index using the SphygmoCor device, model EM3 (ArtCor, Sydney, Australia). Further, retinal vascular images will be made in the right eye with a retina camera (Topcon TRC-NW-300, Topcon Corporation, Tokyo, Japan). The images will be analysed to measure the diameter of the four largest retinal arterioles and venules and to calculate the arteriovenous ratio.

Lifestyle habits

To objectively measure the physical activity level of the women, they will wear an accelerometer (ActiGraph, model wGT3X-BT, Pensacola, FL, USA) for seven full days. Furthermore, women will complete the validated Baecke questionnaire to measure work, sport and leisure activities.[48] To obtain dietary habits, women will complete a seven day nutrition diary. The validated Three Factor Eating Questionnaire (TFEQ) will be used to assess three aspects of eating behaviour: cognitive restraint, disinhibition, and hunger.[49] As a component

of the nutritional status, serum 25-hydroxyvitamin D will be measured using the Immulite-1000. Vitamin D insufficiency is defined as < 50 nmol/L.[50] Smoking habits will be assessed by a questionnaire focussing on smoking behaviour, quitting history, the intention to quit, nicotine dependence and self-efficacy. Biochemical verification of tobacco will be assessed through the piCO^{babyTM} carbon monoxide (CO) monitor (Bedfont® Scientific Ltd., Harrietsham, Maidstone, Kent) by measuring CO in exhaled breath. Long-term use of tobacco will be measured by assessment of cotinin in urine.

Perinatal outcomes

Time to pregnancy is defined as the period between having the concrete wish to become pregnant, to conception. Miscarriage, GDM, GH, preeclampsia, intrauterine growth restriction (IUGR), operative delivery, induction of labour, preterm birth, stillbirth, and congenital malformations will be registered after verifying medical records. Miscarriage is defined as the loss of the foetus until 16 weeks of gestation. GDM, GH, preeclampsia and IUGR will be determined according to the guidelines of the Dutch Society of Obstetrics and Gynaecology. Preterm birth is defined as birth before 37 weeks of gestation.

Postpartum measurements

After childbirth, birth weight, APGAR-score 1 and 5 minutes after birth, SGA, and LGA will be registered. SGA and LGA are defined as birth weight below the 10th percentile, and above the 90th percentile of normal values for gestational age and gender, respectively.[51] The measurements in the child will include obtaining blood samples to determine glucose and insulin levels, and the lipid profile at birth (from cord blood) and at 12 months of age. Lung function at 6 weeks and 12 months postpartum in infants will be assessed by measurements of Functional Residual Capacity, Lung Clearance Index, Tidal Volume and airway resistance using the tremoFlo® C-100 Airwave Oscillometry System (THORASYS, Montreal, QC, Canada). All lung measurements will take place according to international standards.[52] Furthermore, it will be registered whether the child receives (exclusive) breastfeeding.

Sample collection

Samples of the microbial flora, placental tissue and breast milk will be collected and stored. Regarding the microbial flora, stool samples will be collected each 3 months and each trimester during pregnancy from mother and at 6 weeks and 12 months of age from the child, using two collection tubes. When sampled, the participants will be instructed to put the collection tubes in a frozen cool transport container and to store this container in the freezer. Within one week, participants will take the container including the samples to the study site where the samples

will be stored at -80°C until further analysis. Vaginal (of the mother) and oral (of mother and child) microbiome will be collected using a vaginal and throat swab, respectively. These swabs will be stored in transport buffer at -80°C until further analysis. Placental tissue will be collected and stored according to the procedure as described earlier,[53] in order to analyse epigenetic changes. Breast milk will be collected and stored as reported by Lipkie et al.[54], in order to analyse the breast milk composition.

Cost-effectiveness analysis

Questionnaires will be used to collect information on care utilisation. To measure costs, a questionnaire is developed taken into account the various life phases of the women. Relevant costs to be identified include healthcare, patient and family costs, and costs outside the health care sector. To generate quality adjusted life years (QALYs), quality of life is measured by the validated questionnaire EQ-5D-5L.[55 56]

Data management

The data will be collected by using electronic case record forms (MACRO, Elsevier B.V., Amsterdam, the Netherlands) that are adapted to the requirements of the current study. By

using MACRO, the data collected are according to the FAIR (Findable, Accessible, Interoperable and Reusable) criteria.[57] Data will be securely stored for 15 years.

Data analysis

Data will be analysed using SPSS 24.0 for Windows (SPSS Incorporated, Chicago, IL, USA). Descriptive statistics will be performed to describe the baseline characteristics of the study population. Parametric data will be presented as means with standard deviations, non-parametric distributed variables as median with interquartile ranges. Since the design is a repeated-measurement RCT, linear mixed model techniques based on the intention-to-treat principle will be used to analyse the difference between intervention and control group with respect to primary and secondary outcome measurements. This technique corrects for within-subject correlation and deals with missing values at random. Survival analysis will be used to determine the hazard ratio for smoking cessation and time to pregnancy. A p-value <0.05 will be considered statistically significant.

ETHICS

This study will be monitored independently by the Clinical Trial Centre Maastricht. All adverse events will be registered and reported to the medical ethics committee of MUMC+.

DISCUSSION

The main goal of our RCT is to study the effects of a multidisciplinary lifestyle intervention for women with a child wish, and with overweight or obesity with consequently a high risk of perinatal morbidity. The TOP-mums study is one of the first RCT's that studies the effect of a preconceptionally started, multidisciplinary and personalised lifestyle intervention on different behavioural, cardiovascular and perinatal outcomes of mother and child in the period before, during and after pregnancy. There is growing evidence that alterations in maternal metabolic and placental function occur during the first trimester of pregnancy, prior to when most interventions are started.[29 58] To guarantee healthy living from conception on, the lifestyle intervention in this study already starts preconceptionally.

Previous research regarding preconceptional lifestyle interventions is limited and especially the effectiveness of multidisciplinary and customised interventions is unclear.[59 60] When considering interpregnancy weight change, it has been shown that weight loss between pregnancies can reduce the incidence rates of perinatal complications.[22] This paves the way to execute an extensive effect evaluation of the lifestyle intervention in the current study. The study will significantly contribute to the elaboration of the knowledge on the effects of

preconceptional lifestyle guidance on improving health for the current and next generations. One of the strengths of our study is that the lifestyle intervention is developed based on the experiences and wishes of the target group itself and is customised to the personal objectives and wishes. Another asset of this study is the number of data collected, allowing us a better understanding of the consequences and intermediating factors of lifestyle on the health of mother and child.

In this study, most women who are willing to participate might be motivated to change their lifestyle. These women will be allocated to the control group as well, thereby leading to seek for additional lifestyle guidance in this group, potentially diluting the intervention effect. It is known that poor adherence and dropout is frequently experienced in lifestyle interventions. With the processes that are incorporated in the current lifestyle intervention, such as the customised approach and organising activities as much as possible in the direct neighbourhood of participants and at different time slots, the experience of our research group is that we can avoid dropout as much as possible.[61] It is possible that the data collection will be experienced as extensive by the participants. However, the extensive experience of our research group with other lifestyle interventions[62-64] is that participants appreciate monitoring of their health and participants will be motivated by that.

By improving lifestyle in the preconceptional phase the earliest origins of chronic diseases might be tackled. Therefore, the multidisciplinary and customised lifestyle intervention in the TOP-mums study has the potential to benefit global public health by disrupting the vicious circle of transferring harmful lifestyle influences from generation to generation.

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AUTHOR CONTRIBUTIONS

Study concept and design: YT, KvdK, MS, ED, LZ, RST, BK and AV. *Acquisition of data*: YT and LK. *Draft of manuscript and statistical analysis*: YT, KvdK, LK and AV. *Revision of manuscript for important intellectual content*: MS, ED, RST, LZ and BK. All authors gave final approval for publication.

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COMPETING INTERESTS

None

FIGURE LEGENDS

Figure 1: This vicious circle illustrates the intergenerational transmission of diseases. The TOP-mums study focuses on lifestyle improvement and the effects of this lifestyle improvement in the period between preconception and 1 year postpartum as illustrated in the upper part of the circle. 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.

Figure 2: Flow chart of study procedures

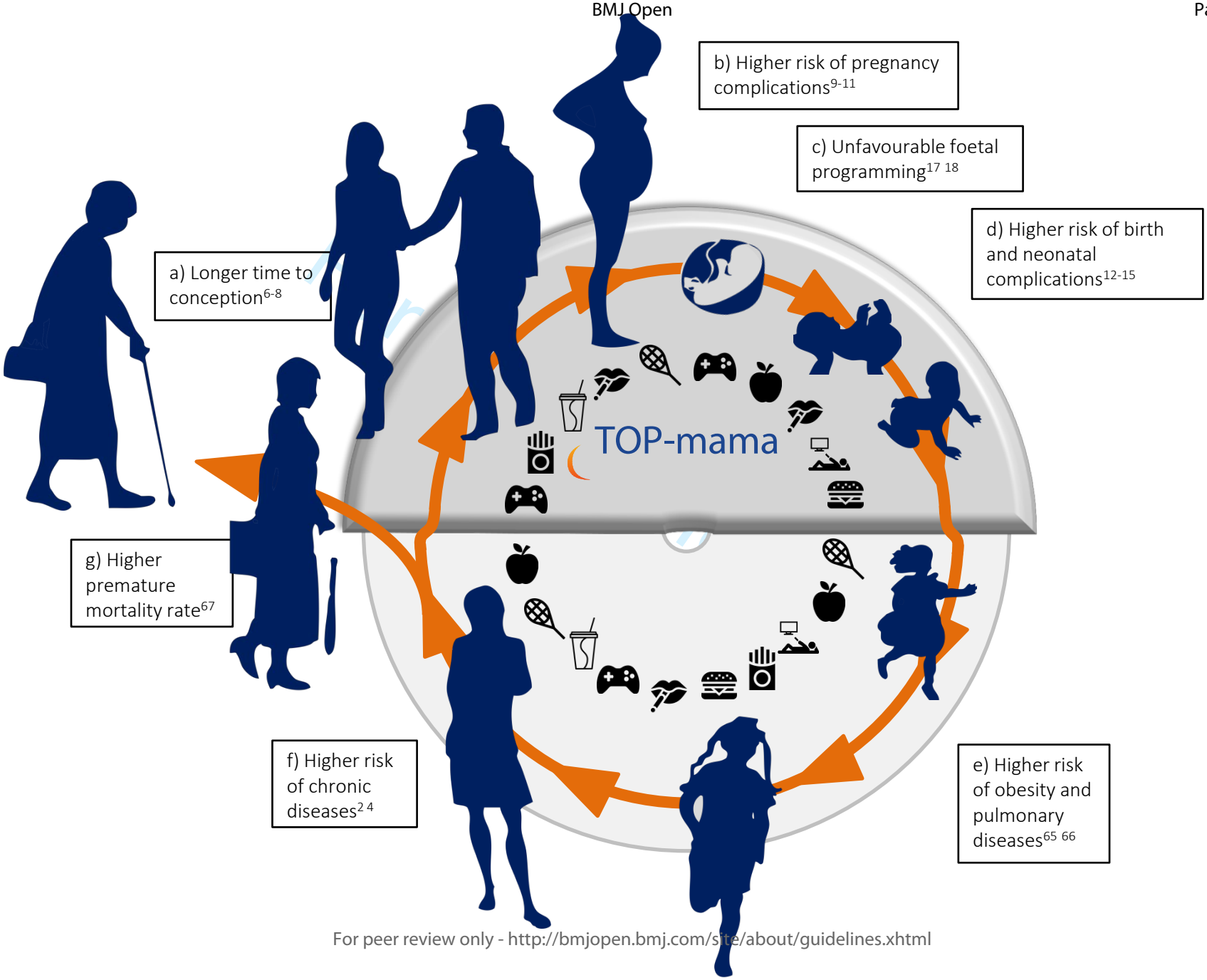
REFERENCES

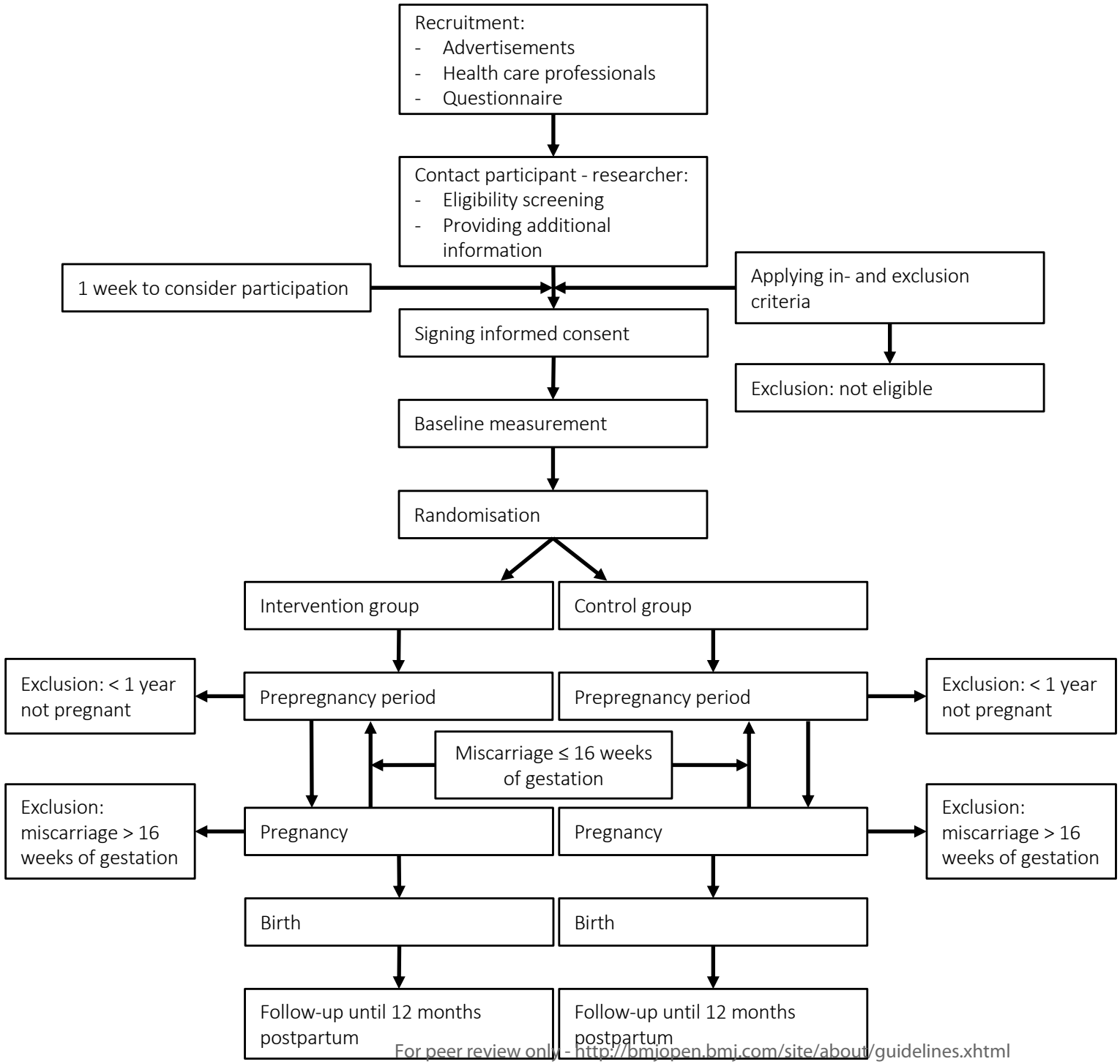
1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2197-223. doi: 10.1016/s0140-6736(12)61689-4I
2. Godfrey KM, Barker DJ. Fetal programming and adult health. *Public Health Nutr* 2001;4(2b):611-24.
3. Godfrey KM, Reynolds RM, Prescott SL, et al. Influence of maternal obesity on the long-term health of offspring. *Lancet Diabetes Endocrinol* 2017;5(1):53-64. doi: 10.1016/s2213-8587(16)30107-3I
4. Gluckman PD, Hanson MA, Cooper C, et al. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 2008;359(1):61-73. doi: 10.1056/NEJMra0708473I
5. Steegers-Theunissen RP, Twigt J, Pestinger V, et al. The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism. *Hum Reprod Update* 2013;19(6):640-55. doi: 10.1093/humupd/dmt041I
6. Hassan MA, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. *Fertil Steril* 2004;81(2):384-92. doi: 10.1016/j.fertnstert.2003.06.027I
7. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. *Hum Reprod Update* 2007;13(3):209-23. doi: 10.1093/humupd/dml056I
8. Brewer CJ, Balen AH. The adverse effects of obesity on conception and implantation. *Reproduction* 2010;140(3):347-64. doi: 10.1530/rep-09-0568I
9. Heslehurst N, Simpson H, Ells LJ, et al. The impact of maternal BMI status on pregnancy outcomes with immediate short-term obstetric resource implications: a meta-analysis. *Obes Rev* 2008;9(6):635-83. doi: 10.1111/j.1467-789X.2008.00511.xI
10. Sebire NJ, Jolly M, Harris JP, et al. Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. *Int J Obes Relat Metab Disord* 2001;25(8):1175-82. doi: 10.1038/sj.ijo.0801670I
11. Torloni MR, Betran AP, Horta BL, et al. Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. *Obes Rev* 2009;10(2):194-203. doi: 10.1111/j.1467-789X.2008.00541.xI
12. Liu P, Xu L, Wang Y, et al. Association between perinatal outcomes and maternal pre-pregnancy body mass index. *Obes Rev* 2016;17(11):1091-102. doi: 10.1111/obr.12455I
13. Stothard KJ, Tennant PW, Bell R, et al. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA* 2009;301(6):636-50. doi: 10.1001/jama.2009.113I
14. Ko TJ, Tsai LY, Chu LC, et al. Parental smoking during pregnancy and its association with low birth weight, small for gestational age, and preterm birth offspring: a birth cohort study. *Pediatr Neonatol* 2014;55(1):20-7. doi: 10.1016/j.pedneo.2013.05.005I
15. Ramachenderan J, Bradford J, McLean M. Maternal obesity and pregnancy complications: a review. *Aust N Z J Obstet Gynaecol* 2008;48(3):228-35. doi: 10.1111/j.1479-828X.2008.00860.xI
16. Eriksson JG, Sandboge S, Salonen MK, et al. Long-term consequences of maternal overweight in pregnancy on offspring later health: findings from the Helsinki Birth Cohort Study. *Ann Med* 2014;46(6):434-8. doi: 10.3109/07853890.2014.919728I
17. Burdge GC, Slater-Jefferies J, Torrens C, et al. Dietary protein restriction of pregnant rats in the F0 generation induces altered methylation of hepatic gene promoters in the adult male offspring in the F1 and F2 generations. *Br J Nutr* 2007;97(3):435-9. doi: 10.1017/s0007114507352392I
18. Gohir W, Ratcliffe EM, Sloboda DM. Of the bugs that shape us: maternal obesity, the gut microbiome, and long-term disease risk. *Pediatr Res* 2014;77:196. doi: 10.1038/pr.2014.169I

19. Nieuwdorp M, Gilijamse PW, Pai N, et al. Role of the microbiome in energy regulation and metabolism. *Gastroenterol* 2014;146(6):1525-33. doi: 10.1053/j.gastro.2014.02.008I
20. Backhed F, Roswall J, Peng Y, et al. Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. *Cell Host Microbe* 2015;17(5):690-703. doi: 10.1016/j.chom.2015.04.004I
21. i-WIP Collaborative group. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. *BMJ* 2017;358:j3119. doi: 10.1136/bmj.j3119I
22. Getahun D, Ananth CV, Peltier MR, et al. Changes in prepregnancy body mass index between the first and second pregnancies and risk of large-for-gestational-age birth. *Am J Obstet Gynecol* 2007;196(6):530.e1-30.e8. doi: 10.1016/j.ajog.2006.12.036I
23. Whiteman VE, Aliyu MH, August EM, et al. Changes in prepregnancy body mass index between pregnancies and risk of gestational and type 2 diabetes. *Arch Gynecol Obstet* 2011;284(1):235-40. doi: 10.1007/s00404-011-1917-7I
24. Perri F, Longo F, Giuliano M, et al. Epigenetic control of gene expression: Potential implications for cancer treatment. *Crit Rev Oncol Hematol* 2017;111:166-72. doi: 10.1016/j.critrevonc.2017.01.020I
25. Poston L, Caleyachetty R, Cnattingius S, et al. Preconceptional and maternal obesity: epidemiology and health consequences. *Lancet Diabetes Endocrinol* 2016;4(12):1025-36. doi: 10.1016/s2213-8587(16)30217-0I
26. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi: 10.1136/bmj.e7586I
27. Mutsaerts MAQ, van Oers AM, Groen H, et al. Randomized Trial of a Lifestyle Program in Obese Infertile Women. *N Engl J Med* 2016;374(20):1942-53. doi: 10.1056/NEJMoa1505297I
28. Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009;374(9702):1677-86. doi: 10.1016/S0140-6736(09)61457-4I
29. Thangaratinam S, Rogozinska E, Jolly K, et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. *BMJ* 2012;344:e2088. doi: 10.1136/bmj.e2088I
30. Hoeger KM, Kochman L, Wixom N, et al. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. *Fertil Steril* 2004;82(2):421-9. doi: 10.1016/j.fertnstert.2004.02.104I
31. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 2003;348(21):2082-90. doi: 10.1056/NEJMoa022207I
32. Vinter CA, Jensen DM, Ovesen P, et al. The LiP (Lifestyle in Pregnancy) study: a randomized controlled trial of lifestyle intervention in 360 obese pregnant women. *Diabetes Care* 2011;34(12):2502-7. doi: 10.2337/dc11-1150I
33. Althuizen E, van der Wijden CL, van Mechelen W, et al. The effect of a counselling intervention on weight changes during and after pregnancy: a randomised trial. *BJOG* 2013;120(1):92-9. doi: 10.1111/1471-0528.12014I
34. Simpson JL. Incidence and timing of pregnancy losses: relevance to evaluating safety of early prenatal diagnosis. *Am J Med Genet* 1990;35(2):165-73. doi: 10.1002/ajmg.1320350205I
35. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, et al. Subfecundity in overweight and obese couples. *Hum Reprod* 2007;22(6):1634-7. doi: 10.1093/humrep/dem035I
36. Hull MG, North K, Taylor H, et al. Delayed conception and active and passive smoking. The Avon Longitudinal Study of Pregnancy and Childhood Study Team. *Fertil Steril* 2000;74(4):725-33.
37. Burke BL, Arkowitz H, Menchola M. The efficacy of motivational interviewing: a meta-analysis of controlled clinical trials. *J Consult Clin Psychol* 2003;71(5):843-61. doi: 10.1037/0022-006x.71.5.843I

38. Miller WR, Rollnick S. Motivational Interviewing, Second Edition: Preparing People for Change: Guilford Publications 2002.
39. Van Dijk MR, Huijgen NA, Willemsen SP, et al. Impact of an mHealth Platform for Pregnancy on Nutrition and Lifestyle of the Reproductive Population: A Survey. *JMIR Mhealth Uhealth* 2016;4(2):e53. doi: 10.2196/mhealth.5197I
40. Van Dijk MR, Koster MP, Rosman AN, et al. Opportunities of mHealth in Preconception Care: Preferences and Experiences of Patients and Health Care Providers and Other Involved Professionals. *JMIR Mhealth Uhealth* 2017;5(8):e123. doi: 10.2196/mhealth.7834I
41. van Dijk MR, Koster MPH, Willemsen SP, et al. Healthy preconception nutrition and lifestyle using personalized mobile health coaching is associated with enhanced pregnancy chance. *Reprod Biomed Online* 2017;35(4):453-60. doi: 10.1016/j.rbmo.2017.06.014I
42. van Dijk MR, Oostingh EC, Koster MP, et al. The use of the mHealth program Smarter Pregnancy in preconception care: rationale, study design and data collection of a randomized controlled trial. *BMC Pregnancy Childbirth* 2017;17(1):46. doi: 10.1186/s12884-017-1228-5I
43. Stichting Voedingscentrum Nederland. De Schijf van Vijf [18-07-2018]. Available from: https://www.voedingscentrum.nl/nl/gezond-eten-met-de-schijf-van-vijf.aspx accessed 18-07-2018.
44. Institute of Medicine. The National Academies Collection: Reports funded by National Institutes of Health. In: Rasmussen KM, Yaktine AL, eds. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington (DC): National Academies Press (US) National Academy of Sciences. 2009.
45. Shiri R, Coggon D, Falah-Hassani K. Exercise for the prevention of low back and pelvic girdle pain in pregnancy: A meta-analysis of randomized controlled trials. *Eur J Pain* 2018;22(1):19-27. doi: 10.1002/ejp.1096I
46. Westerterp KR, Wouters L, van Marken Lichtenbelt WD. The Maastricht protocol for the measurement of body composition and energy expenditure with labeled water. *Obes Res* 1995;3 Suppl 1:49-57.
47. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28(7):412-9.
48. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* 1982;36(5):936-42. doi: 10.1093/ajcn/36.5.936I
49. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J Psychosom Res* 1985;29(1):71-83.
50. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. *Lancet* 1998;351(9105):805-06. doi: 10.1016/S0140-6736(05)78933-9I
51. Visser GH, Eilers PH, Elferink-Stinkens PM, et al. New Dutch reference curves for birthweight by gestational age. *Early Hum Dev* 2009;85(12):737-44. doi: 10.1016/j.earlhumdev.2009.09.008I
52. Stocks J, Sly P.D., Tepper R.S., et al. Infant respiratory function testing. *Wiley-Liss* 1996
53. Nelissen EC, Dumoulin JC, Busato F, et al. Altered gene expression in human placentas after IVF/ICSI. *Hum Reprod* 2014;29(12):2821-31. doi: 10.1093/humrep/deu241I
54. Lipkie TE, Morrow AL, Jouni ZE, et al. Longitudinal Survey of Carotenoids in Human Milk from Urban Cohorts in China, Mexico, and the USA. *PLoS One* 2015;10(6):e0127729. doi: 10.1371/journal.pone.0127729I
55. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-xI
56. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013;22(7):1717-27. doi: 10.1007/s11136-012-0322-4I

57. Wilkinson MD, Dumontier M, Aalbersberg IJ, et al. The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* 2016;3:160018. doi: 10.1038/sdata.2016.18I
58. Catalano P, deMouzon SH. Maternal obesity and metabolic risk to the offspring: why lifestyle interventions may have not achieved the desired outcomes. *Int J Obes* 2015;39(4):642-9. doi: 10.1038/ijo.2015.15I
59. Temel S, van Voorst SF, Jack BW, et al. Evidence-based preconceptional lifestyle interventions. *Epidemiol Rev* 2014;36:19-30. doi: 10.1093/epirev/mxt003I
60. Hillemeier MM, Downs DS, Feinberg ME, et al. Improving women's preconceptional health: findings from a randomized trial of the Strong Healthy Women intervention in the Central Pennsylvania women's health study. *Womens Health Issues* 2008;18(6 Suppl):S87-96. doi: 10.1016/j.whi.2008.07.008I
61. Burgess E, Hassmen P, Pumpa KL. Determinants of adherence to lifestyle intervention in adults with obesity: a systematic review. *Clin Obes* 2017;7(3):123-35. doi: 10.1111/cob.12183I
62. Rijks JM, Plat J, Mensink RP, et al. Children With Morbid Obesity Benefit Equally as Children With Overweight and Obesity From an Ongoing Care Program. *J Clin Endocrinol Metab* 2015;100(9):3572-80. doi: 10.1210/jc.2015-1444I
63. Willeboordse M, van de Kant KDG, Tan FE, et al. A Multifactorial Weight Reduction Programme for Children with Overweight and Asthma: A Randomized Controlled Trial. *PLoS One* 2016;12(7):e0181130. doi: 10.1371/journal.pone.0157158I
64. Hutchinson SG, van Breukelen G, van Schayck CP, et al. Motivational interviewing and urine cotinine feedback to stop passive smoke exposure in children predisposed to asthma: a randomised controlled trial. *Sci Rep* 2017;7(1):15473. doi: 10.1038/s41598-017-15158-2I
65. Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2001;163(2):429-36. doi: 10.1164/ajrccm.163.2.2006009I
66. Scholtens S, Wijga AH, Brunekreef B, et al. Maternal overweight before pregnancy and asthma in offspring followed for 8 years. *Int J Obes* 2010;34(4):606-13. doi: 10.1038/ijo.2009.194I
67. Di Angelantonio E, Bhupathiraju SN, Wormser D, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;388(10046):776-86. doi: 10.1016/S0140-6736(16)30175-1I





SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 3
	2b	All items from the World Health Organization Trial Registration Data Set	Page 3
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	Page 20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, page 20
	5b	Name and contact information for the trial sponsor	Page 20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 5 & 6
	6b	Explanation for choice of comparators	Page 7
Objectives	7	Specific objectives or hypotheses	Page 7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 7 & 8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 18 & 19
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 12-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Not applicable
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Not applicable
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 18 & 19

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Not applicable
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not applicable

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	-
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page 16

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

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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

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ABSTRACT

Introduction: Periconceptional obesity and smoking are associated with a higher risk of adverse perinatal outcomes such as gestational diabetes mellitus (GDM), preeclampsia, large for gestational age (LGA), operative delivery and preterm birth. Lifestyle interventions during pregnancy have resulted in insufficient effects on reducing these perinatal complications. A few reasons for this disappointing effect can be suggested: 1) the time period during pregnancy for improvement of developmental circumstances is too short; 2) the periconception period in which complications originate is not included; and 3) lifestyle interventions may not have been sufficiently multidisciplinary and customised. A preconceptional lifestyle intervention may potentially be better able to achieve reduction of perinatal complications. Therefore, the aim of the TOP-mums study is to evaluate the effect of a preconceptionally started lifestyle intervention on lifestyle behaviour change.

Methods and analysis: This protocol outlines a non-blinded, randomised controlled trial. One hundred and twelve women (18-40 years of age) who plan to conceive within one year, with overweight or obesity (Body Mass Index (BMI) ≥25.0 kg/m^2) will be randomised to either the intervention or control group. The intervention group will receive a multidisciplinary, customised lifestyle intervention stimulating physical activity, a healthy diet and, if applicable, smoking cessation. The control group will receive care as usual. The lifestyle intervention and

monitoring will take place until 12 months postpartum. The primary outcome is difference in weight in kg from baseline to 6 weeks postpartum. Secondary outcomes are gestational weight gain, postpartum weight retention, smoking cessation, dietary and physical activity habits. Furthermore, exploratory outcomes include body composition, cardiometabolic alterations, time to pregnancy, need for assisted reproductive technologies, perinatal complications of mother and child, and lung function of the child. Vaginal and oral swabs, samples of faeces, breast milk, placenta and cord blood will be stored for evaluation of microbial flora, epigenetic markers and breast milk composition. Furthermore, a cost-effectiveness analysis will take place.

Ethics and dissemination: Ethical approval was obtained from the Medical Ethical Committee of Maastricht University Medical Centre+ (NL52452.068.15/METC152026). Knowledge derived from this study will be made available by publications in international peer reviewed scientific journals and will be presented at (inter)national scientific conferences. A dissemination plan for regional and national implementation of the intervention is developed.

Trial registration number: ClinicalTrials.gov NCT02703753.

Keywords: Lifestyle, preconception, non-communicable diseases, pregnancy complications

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This randomised controlled trial is innovative by evaluating effects of a lifestyle intervention that starts preconceptionally and continues until one year postpartum;
- The strength of the intervention is that it's multidisciplinary and personalised approach, taken into account the wishes, needs and opportunities of the women at risk;
- This study will collect a broad range of data, including longitudinal data regarding mechanisms hypothesised to be involved in the intergenerational transmission of diseases, which is scarcely studied yet and allows the generation of new hypotheses;
- Women who are willing to participate in the study are potentially more motivated to change their lifestyle, also when allocated to the control group;
- The sample size calculated to answer the primary research question may be relatively small in order to achieve sufficient power for the effect evaluation of some outcome measurements, which therefore must be seen as exploratory.

INTRODUCTION

Worldwide, the prevalence of chronic diseases such as cardiovascular diseases, dyslipidaemia and diabetes mellitus is increasing. The rising burden from these chronic diseases imposes new challenges for health care.[1] Key risk factors in the development of chronic diseases are lifestyle habits such as smoking, lack of physical activity, unhealthy diet and being overweight. As illustrated in Figure 1, there is increasing evidence suggesting that the detrimental effects of being exposed to a certain lifestyle originate from the periconceptional period.[2-5] By tackling its earliest origins, improving lifestyle preconceptionally is hypothesised to benefit global public health by addressing the increasing problem of chronic diseases.

Overweight and obesity before and during pregnancy negatively impact fertility,[6-8] pregnancy and birth outcomes,[4 9] and increase the risk for the development of chronic disease for both mother and child.[10-12] During pregnancy, women who are overweight or obese are at increased risk to develop complications such as gestational hypertension (GH), preeclampsia and gestational diabetes mellitus (GDM), and are more often in need of emergency caesarean delivery.[13 14] In addition, maternal obesity is associated with a higher risk for adverse perinatal outcomes such as congenital abnormalities, large for gestational age (LGA), and birth trauma

as consequence of shoulder dystocia.[15 16] Besides, neonates of women with obesity are more likely to be admitted to the neonatal intensive care unit.[17] In addition to overweight, it is clearly established that maternal smoking negatively affects the health of mother and new-born. Moreover, maternal smoking decreases fertility[18] and intra-uterine exposure to smoking is associated with a higher risk for small for gestational age (SGA) and preterm birth.[19]

The risk of adverse events among offspring can extend through adulthood, demonstrating a vicious circle of intergenerational transmission of diseases.[3 5 20] Several studies suggest that intra-uterine exposure to an unhealthy lifestyle can increase the risk of cardiovascular, metabolic and endocrine disease in adult life by unfavourable foetal programming.[2 5] Studies in animals indicate that epigenetic processes might be an important link between maternal lifestyle habits, and the risk for developing obesity and chronic diseases in adult offspring. Epigenetic processes modulate gene transcription, establishing a detrimental epigenome during embryogenesis and early development of the foetus.[21] Furthermore, recent research suggests a role for the microbiota in the intergenerational transmission of obesity.[22] Bacterial diversity is influenced by obesity and gestational weight gain.[23] It is hypothesised that the transfer of an obesogenic microbial flora from mother to child during birth contributes to the intergenerational transmission of diseases.[24]

In an attempt to prevent perinatal complications, previous studies investigated the effect of lifestyle behaviour modification during pregnancy. Although these interventions were successful in limiting gestational weight gain, they were unsuccessful in reducing GDM, preeclampsia and LGA in women with obesity.[25] It could be suggested that starting during pregnancy, the time span to achieve sufficient impact on pregnancy outcomes might be too short. In addition, most study protocols did not include a multidisciplinary and customised approach and did not take into account the effects of lifestyle during the periconception period in which perinatal complications often originate. Data from large population-based studies have shown that reducing BMI from overweight or obesity before the first pregnancy to normal weight before the subsequent pregnancy decreased the risk of GDM and LGA.[26 27] Therefore, a lifestyle intervention that starts during the preconception phase might be promising in reducing pregnancy and birth complications and thereby provide a more promising start for the future generation.

Aim

The primary aim of this study is to evaluate the impact of a preconception lifestyle intervention on weight change in women with overweight or obesity and with a child wish. Secondary study

aims are to evaluate the effect of the lifestyle intervention on gestational weight gain, postpartum weight retention and lifestyle habits such as physical activity, dietary intake and smoking behaviour. In addition, we will explore the effects of the intervention on cardiometabolic alterations, body composition, time to pregnancy, need for assisted reproductive technologies, and perinatal complications such as GDM, GH, preeclampsia, SGA, LGA and preterm birth, cardiometabolic alterations and lung function in the child. Furthermore, changes in the microbial flora, epigenetics and breast milk composition will be evaluated. Finally, a cost-effectiveness analysis of the lifestyle intervention will be conducted.

METHODS AND ANALYSIS

This protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement (see Supplement 1: SPIRIT checklist).[28] The TOP-mums study was approved by the Medical Ethical Committee of the Maastricht University Medical Centre+ (Maastricht UMC+; NL52452.068.15/METC152026).

Study design

This study is a randomised controlled trial (RCT) in which the participants and investigators will not be blinded due to pragmatic reasons. Participants will be randomised 1:1 in either the intervention or control group using block randomisation, with random block sizes of 2, 4 or 6. Randomisation will be stratified for overweight (BMI 25.0-29.9 kg/m^2), obesity (BMI ≥30.0 kg/m^2), and smoking status. The study will start before conception and will continue during pregnancy until one year after delivery. The lifestyle intervention and follow-up will end for women who are not pregnant within one year after randomisation and in case of a foetal demise between 16 and 24 weeks of gestational age. In case of a miscarriage before 16 weeks of gestational age, women will continue their participation in the study in order to follow-up a potential second pregnancy.

After childbirth, both parents will be informed about participation of their child in the study both verbally as well as by the information letter. Participation of the child will only be feasible when both parents sign informed consent (see Supplement 2: Inform consent form child). When women/parents decide to quit participation, they will be asked to continue fulfilling the cost and quality of life questionnaires. This will enable us to perform an adequate as possible cost-effectiveness analysis. A flow chart of these procedures is presented in Figure 2.

Setting and study population

The study will be conducted in the South of Limburg, the Netherlands and is initiated and coordinated by Maastricht UMC+. Women will be eligible to participate in this study when meeting the following criteria: planning to conceive within one year, 18-40 years of age, and having a BMI ≥25.0 kg/m². Smoking is neither an inclusion nor an exclusion criterion. Only women who are able to read and speak Dutch and/or English will be included. Being treated in a fertility clinic is not an exclusion criterion. Women will be excluded in case it is known that they had a positive pregnancy test at the moment of randomisation. In addition, women will be excluded in case of having a haemodynamically significant heart disease, restrictive lung disease, congenital metabolic disease, diagnosed as intellectually disabled according to the DSM5 criteria,[29] bariatric surgery in the past, and having diabetes type II dependent on medication.

Recruitment

Multiple recruitment strategies will be used to reach an adequate number of potential participants (see sample size). Recruitment will take place in the region of Maastricht, South of Limburg, the Netherlands. In 2018, 1,400 children were born in this region.[30] First, gynaecologists, midwifes, general practitioners, and the Dutch youth health care system (a

preventive health care system available for all children aged 0–19 years in the Netherlands) will be involved in recruiting women. At Maastricht UMC+, women may visit a gynaecologist in relation to assisted reproductive technologies or may visit the preconception outpatient clinic because they are at risk for developing pregnancy complications. In addition, women may visit their midwife with regard to the "child-wish consultation" or their general practitioner for removing or discussing their birth control. Women in the period between two pregnancies will also visit the Dutch youth health care system with their previous child(ren). In addition to recruitment via health care providers, advertisements will be placed in newspapers and magazines distributed in de region of Maastricht, and on social media. Social media campaigns will focus on women of childbearing age living in the region of Maastricht. Furthermore, advertisements will be placed on websites targeting on pregnant women and young mothers. Based on the responses we will receive on each type of advertisement, we will determine which kind of campaign is most successful in reaching the target population. Subsequently, we will focus on the most successful types of campaign. Third, in order to conduct another – cross-sectional – study (manuscript in preparation), a questionnaire was sent to women of reproductive age in the region. Simultaneously, women were asked if they were interested in being approached for participation in the current study. Women who fulfil the inclusion criteria and who gave consent, will be contacted for participation.

Sample size

A sample size calculation was conducted for the primary outcome measure, defined as the mean difference in body weight in kg from baseline to 6 weeks postpartum. In a previous study that evaluated the effect of a lifestyle intervention in subfertile women, a mean reduction of 3.4 kg resulted in a higher natural conception rate.[31] Further, a weight reduction of 5-10% was associated with a reduction of the incidence of type 2 diabetes in adults at risk due to a BMI ≥24.0 kg/m².[32] During pregnancy, lifestyle interventions resulted in a 1.5 kg reduction in gestational weight gain.[33] In some studies, this weight reduction was associated with a lower prevalence of preeclampsia.[33] Taken these previous results into account, our research group determined a mean difference of 5 kg with a SD of 7 kg between the study groups as clinically relevant. For the sample size calculation, an alpha of 0.05 (two-sided) and a power of 80% is used. Taken into account a drop-out rate of 44% (based on drop-out rates of other lifestyle interventions (22%),[31 34-37] foetal demise after 16 weeks of gestation (1%),[38 39] and time to pregnancy >12 months (21%)[7 40 41]), a total of 110 women should start the study to be able to detect a mean difference of 5 ± 7 kg with 62 women required for analysis.

Procedure

When women indicate that they are interested to participate in the TOP-mums study, they will be informed on the study by telephone after which they receive a comprehensive information letter. During the telephone contact, eligibility will be determined based on inclusion and exclusion criteria. After information is provided, at least one week of consideration to participate in the study will follow. When women decide to participate in the study, the baseline measurement will be arranged. Before the baseline measurement will take place, women will be asked to sign the informed consent form (see Supplement 3: Inform consent form women planning to conceive). In addition, height and weight will be measured to confirm the inclusion criteria of BMI ≥25.0 kg/m². Thereafter, randomisation by the software program ALEA (ALEA Clinical B.V., Abcoude, the Netherlands) allocates participants to either the intervention or control group, the latter receiving care as usual.

Care as usual

Both study groups will receive care as usual. Additional to usual care, women in the intervention group will receive the lifestyle intervention as described below. In the Netherlands, usual care for women before pregnancy includes access to the general practitioner and "child wish consultations" by a midwife. In addition, assisted reproductive technologies are part of care as usual for subfertile women according to the Dutch infertility guidelines.[42] Assisted

reproductive technologies according to the Dutch guidelines will continue during study participation. Pregnant women have access to their general practitioner and their midwife and/or gynaecologist. After pregnancy, maternity care in the first week postpartum at home will support breastfeeding. In addition, frequent consultations will take place at the youth health care division and for both mother and child access to the general practitioner is ensured. During these three periods, health care professionals will give lifestyle advices (according to national guidelines) when women specifically request for help regarding this topic or when health care professionals have other reasons for giving this advice (for example in case women have a cardiometabolic risk factor). In addition, health care professionals are not restricted to refer women to additional lifestyle guidance (e.g. by a dietician or lifestyle coach) when needed. Use of additional lifestyle guidance in the control group will be registered.

Lifestyle intervention

The TOP-mums lifestyle intervention is multidisciplinary and stimulates physical activity and a healthy diet, and, if applicable, smoking cessation. A qualitative study to determine the needs and wishes of the women in the target population was executed by our research group (results not published yet). Results are incorporated in the intervention. Each woman will be assigned to her own personal lifestyle coach, who will coordinate and guide the woman through her

personal program. Women will visit the personal lifestyle coach frequently (every month to once in three months [see Supplement 4: Schedule consultations with personal lifestyle coach and dietician]). The personal lifestyle coach has a medical background and is trained in motivational interviewing. Women will not receive a fixed schedule, but their program will be determined based on their wishes, needs and opportunities using motivational interviewing by the personal lifestyle coach.[43 44] This involves three steps: 1) lifestyle habits will be assessed by a nutrition diary, questionnaires and an activity tracker at the start of the lifestyle intervention. Based on this assessment, potential improvements in lifestyle habits will be determined; 2) together with the woman, it will be determined which lifestyle improvement should be tackled first and goals will be formulated; 3) it will be discussed with the woman which (combination) of supporting programs, as elaborated below, will be valuable in achieving her goals and will best suit within her daily life. The program will cover the periods before, during and after pregnancy. Each phase will be accompanied by specific lifestyle advices. This lifestyle intervention is innovative by the adaptive and proactive approach and the structured offer of lifestyle guidance. In this manner, women are supported with easily accessible lifestyle guidance.

Smarter pregnancy

Each woman will be provided with a subscription to the mHealth program Smarter Pregnancy (Slimmere Zorg B.V., Bussum, the Netherlands). This coaching program supplies personal coaching of 26 weeks, based on current personal circumstances, pregnancy status, nutrition and lifestyle. It was demonstrated to improve nutrition and other lifestyle behaviours.[45-48] The tailored coaching includes a maximum of three digital posts per week, containing advices, seasonal recipes for healthy meals and additional questions addressing lifestyle behaviour, taking into account pregnancy status.

Psychological guidance

For women who suffer from eating disorders in combination with overweight or obesity, psychological support can help with sustainable improvement of lifestyle. In order to determine the appropriate supporting programs that will meet the wishes and needs of the women, a standardised quick-scan on eating habits (see Supplement 5: Screening eating disorders) will be answered by the women. Results will be assessed by a psychologist and in case an eating disorder might be the case, a consultation will take place by a psychologist to determine whether a woman is suffering from an eating disorder according to the DSM-5 criteria.[29] The cornerstone of the guidance is the treatment of the eating disorder and possible other psychological comorbidities (e.g. depression). Moreover, sustainable change of lifestyle, and

improvement of social and labour participation will be targeted. Cognitive behaviour therapy, cue exposure and system therapy are techniques that will be used. In general, this involves coaching sessions two to three times a week, for four months. The psychological guidance will be delivered by a team of psychologists, dieticians and physiotherapists at a mental health care institution specialised in the treatment of obesity in combination with eating disorders.[49]

Dietary guidance

Individualised sessions will take place with a dietician approximately every one or two months, providing advices to improve the intake of dairy products, fruit and vegetables, while decreasing the intake of high-energy foods with little nutritional value. Diet advices are according to the recommendations of the Netherlands Nutrition Centre Foundation[50] and the intervention will target a healthy diet, without extreme regimens. During pregnancy, a target will be set for a maximum gestational weight gain, aiming at staying within the Institute of Medicine guidelines.[51] In the postpartum period, consultations will be directed towards dietary advices for mother and child. Breastfeeding will be encouraged by a trained lactation consultant. Frequency of consultations is not fixed and can be adopted to the wishes and needs of the women, but a guideline is provided in Supplement 4.

Physical activity

To support weekly physical activity at moderate intensity, a physical activity program conducted by professionals trained in physical education will be offered. This physical activity program will be offered by the sports department of the municipality of Maastricht. In the preconceptional period, the physical activity program will focus on improving aerobic capacity, muscle strengthening and increasing energy expenditure. The activities will be diverse to make it attractive for the women. Furthermore, the activities will take place on different time slots and different locations in order to make it as easy as possible to join one of the activities. During pregnancy, sessions will be conducted by a ZwangerFit® trained physiotherapist. ZwangerFit® is a course that focuses on physical fitness, muscle strengthening, coordination and stabilisation, especially for the pelvic muscles. It is previously shown that these exercises reduce the risk of low back pain, and sick leave because of lumbopelvic pain during pregnancy.[52] At 6 weeks postpartum, individual sessions will catch up until 9 months postpartum, by a paediatric physiotherapist, focussing on the mother having fun in playing with their child, emotional bonding, and stimulating motor development. These sessions will take place in the safety of the home of mother and child. The paediatric physiotherapist will discuss which kind of activities mothers wishes to catch up after childbirth in addition to the individual consultations such as swimming classes or baby mindfulness classes.

Smoking cessation

To target smoking cessation, the personal lifestyle coach will apply motivational interviewing techniques to support women to quit smoking. If necessary, women can be referred to a smoking cessation coach for more extensive guidance.

Outcomes

Anthropometric, cardiometabolic, lifestyle habits, perinatal and postpartum outcomes will be measured and registered, and samples collected to determine the effects of the lifestyle intervention on health of the women and child (see Table 1 for an overview). Study visits will take place at Maastricht UMC+ and will take place during consultation with the personal lifestyle coach in order to minimise the time investment as much as possible for the women. In this study, health checks will be performed outside the scope of usual clinical practice. Therefore, the measurements performed within the context of this study 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.

The first step in determining what the effect is of the lifestyle intervention proposed in this study, is to examine the effect of the intervention on lifestyle behaviour change. It is assumed that lifestyle behaviour change results in weight change and weight change is an objectively outcome measurement. Based on the expectation that weight change will result in cardiometabolic changes, the next step is to study whether weight change has influence on secondary and exploratory outcomes.

Table 1: Overview of the measurements at different time points during the study

		Preconception						Pregnancy								Postpartum				
	Baseline	*1 month*	*2 months*	*3 months*	*6 months*	*9 months*	*12 months*	*6 weeks*	*12 weeks*	*20 weeks*	*26 weeks*	*32 weeks*	*36 weeks*	*40 weeks*	*Birth*	*6 weeks*	*3 months*	*6 months*	*9 months*	*12 months*
Anthropometric measurements																				
Weight, BMI, waist and hip circumference mother	x	x	x	x	x	x	x	x	x	x		x	x	x		x	x	x	x	x
Body composition mother	x											x						x		
Weight, height and BMI child																x	x	x	x	x
Cardiometabolic outcomes																				
Blood pressure mother	x	x	x	x	x	x	x	x	x	x		x	x	x		x	x	x	x	x
Pulse wave velocity mother	x			x	x		x	x		x		x						x		x
Retinal image mother	x			x	x		x	x		x		x						x		x
Glucose, insulin levels, lipid profile, liver enzymes mother				x				x		x		x					x	x		x
OGTT mother	x										x									x
Glucose, insulin levels, lipid profile child (cord blood)															x					
Glucose, insulin, lipid profile child																				x
Lifestyle habits																				
Accelerometer mother	x			x			x	x				x					x			x

Baecke questionnaire mother	x			x			x	x			x					x				x
Nutrition diary mother	x			x			x	x			x					x				x
Three Factor Eating Questionnaire mother	x			x			x	x			x					x				x
Vitamin D mother	x										x									
Smoking behaviour questionnaire mother	x	x	x	x	x	x	x	x	x	x		x	x	x		x	x	x	x	x
CO measurement mother	x	x	x	x	x	x	x	x	x	x		x	x	x		x	x	x	x	x
Urine cotinin mother	x			x				x		x		x				x				x
Feeding pattern child																x	x	x	x	x
Perinatal outcomes																				
Time to pregnancy								x												
Need for assisted reproductive technologies								x												
Miscarriage										x										
Pregnancy complications (GDM, GH, preeclampsia, IUGR)												x	x	x						
Method of delivery															x					
Induction of labour															x					
Postpartum measurements																				
Birth weight															x					
Gestational age															x					
APGAR-score															x					
Stillbirth															x					
Sample collection																				
Microbiome sampling mother	x			x	x	x	x	x		x		x					x	x	x	x
Epigenetic sampling															x					
Breast milk sampling																x				
Microbiome sampling child																x				x
Cost-effectiveness analysis																				
Cost questionnaire	x			x	x	x	x	x		x		x					x	x	x	x
EO-5D-5L	x			x	x	x	x	x		x		x					x	x	x	x

When women become pregnant at a certain time point without completion of all preconception measurements, the remaining preconception measurements will be cancelled. Women will continue the measurements belonging to the pregnancy period. The same procedure will take place when women

give birth before 40 weeks of gestational age. Abbreviations: BMI, body mass index; CO, carbon monoxide; EQ-5D-5L, Quality of life measurement; GDM, gestational diabetes mellitus; GH, gestational hypertension; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test.

Anthropometric measurements

Body weight of the women will be assessed in underwear with no shoes in kilogram to the nearest 0.1 kilograms using a medical calibrated weight scale (Model 799, seca gmbh & co. kg., Chino, USA), at each study visit. Height will be determined by a stadiometer (Model 220, seca gmbh & co. kg., Chino, USA) calibrated in 0.1 cm intervals. BMI will be calculated as the weight in kg divided by height in meters squared. Gestational weight gain is defined as weight in kg from 6 to the last prenatal study visit and will be compared to the Institute of Medicine guidelines.[51] Postpartum weight retention is defined as the difference in weight in kg between 6 weeks of gestational age and 6 months postpartum.

The waist and hip circumference will be measured with a non-elastic tape at the end of a natural breath at midpoint between the top of the iliac crest and the lower margin of the last palpable rib respectively on the widest point of the hip, standing on both feet equally with arms hanging down. The waist/hip ratio will be calculated. Furthermore, the body composition (i.e. fat and fat-free mass) will be measured at three time points during the study using the technique with water labelled with deuterium according to the Maastricht protocol.[53] During

pregnancy, adjustments to the calculation of fat and fat-free mass will be applied to take into account the gestational specific fat-free mass in which the water labelled with deuterium easily escape.[54 55]

Lifestyle habits

To objectively measure the physical activity level of the women, they will wear an accelerometer (ActiGraph, model wGT3X-BT, Pensacola, FL, USA) for seven full days. Furthermore, women will complete the validated Baecke questionnaire to measure work, sport and leisure activities.[56] To obtain dietary habits, women will complete a seven day nutrition diary. The validated Three Factor Eating Questionnaire (TFEQ) will be used to assess three aspects of eating behaviour: cognitive restraint, disinhibition, and hunger.[57] As a component of the nutritional status, serum 25-hydroxyvitamin D will be measured using the Immulite-1000. Vitamin D insufficiency is defined as < 50 nmol/L.[58] Smoking habits will be assessed by a questionnaire focussing on smoking behaviour, quitting history, the intention to quit, nicotine dependence and self-efficacy. Biochemical verification of tobacco will be assessed through the piCO^{babyTM} carbon monoxide (CO) monitor (Bedfont® Scientific Ltd., Harrietsham, Maidstone, Kent) by measuring CO in exhaled breath. Long-term use of tobacco will be measured by assessment of cotinin in urine.

Cardiometabolic outcomes

Fasting blood samples will be taken at different time points before, during and after pregnancy to determine blood glucose and insulin levels, lipid profile and liver enzymes. Fasting plasma glucose will be determined using the Cobas 8000 modular analyser (F. Hoffmann-La Roche Ltd., Basel, Swiss) and serum insulin concentrations using the Immulite-1000 (Siemens Healthcare Diagnostics, Erlangen, Germany). Based on this, the homeostatic model assessment of insulin resistance (HOMA-IR) will be calculated according to fasting glucose (mmol/L)*(fasting insulin (μU/L)/22.5).[59] All participants will have a 75 gram oral glucose tolerance test at baseline, 26 weeks of gestational age, and 12 months postpartum. Blood glucose and insulin concentrations will be measured after 1 and 2 hours. Fasting serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, serum alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) concentrations, will be determined using the Cobas 8000 modular analyser.

Cardiovascular alterations will be measured by systolic and diastolic blood pressure (SBP and DBP), using a validated automatic device (A&D Medical UA-789XL, Saitama, Japan) on the

left arm after 5-10 minutes rest in a sitting position for four times, with one minute rest in between. Mean SBP and DBP of the three last measurements will be calculated. 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,[60 61] these measurements are included in this study. Arterial stiffness will be assessed by the carotid-femoral and carotid-radial pulse wave velocity and Augmentation Index using the SphygmoCor device, model EM3 (ArtCor, Sydney, Australia). Further, retinal vascular images will be made in the right eye with a retina camera (Topcon TRC-NW-300, Topcon Corporation, Tokyo, Japan). The images will be analysed to measure the diameter of the four largest retinal arterioles and venules and to calculate the arteriovenous ratio.[60 61]

Perinatal outcomes

Time to pregnancy is defined as the period between having the concrete wish to become pregnant, to conception. The need for assisted reproductive technologies and the reason for this (e.g. because of chronic anovulation or unsuccessfully tried to conceive for at least 12 months despite an ovulatory cycle) will be registered. Miscarriage, GDM, GH, preeclampsia,

intrauterine growth restriction (IUGR), operative delivery, induction of labour, preterm birth, stillbirth, and congenital malformations will be registered after verifying medical records. Miscarriage is defined as the loss of the foetus until 16 weeks of gestation. GDM, GH, preeclampsia and IUGR will be determined according to the guidelines of the Dutch Society of Obstetrics and Gynaecology. GDM is defined as a diagnosis of hyperglycaemia during pregnancy, in a woman without pre-existing diabetes mellitus. The Dutch national guideline is in line with the World Health Organization guideline on Diagnosis and Classification of Diabetes Mellitus, which defined hyperglycaemia as the presence of either a fasting plasma glucose ≥7.0 mmol/l or 2-hour plasma glucose ≥7.8 mmol/l following a 75 g oral glucose tolerance test.[62 63] GH is defined as systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least 90 mmHg after 20 weeks of gestational age.[64] Preeclampsia is defined as GH accompanied by proteinuria (at least 300 mg protein in a 24-hour urine collection).[64] IUGR is defined as estimated foetal weight <p10, abdominal circumference <p10 or a decrease in growth of at least 20 percentiles within a minimal time frame of two weeks.[65] Preterm birth is defined as birth before 37 weeks of gestation and will subdivided in spontaneous (delivery started by primary contractions or spontaneous rupture of membranes) and indicated (including the performance of a caesarean delivery before onset of labour or induction of labour) preterm birth.

Postpartum measurements

After childbirth, birth weight, APGAR-score 1 and 5 minutes after birth, SGA, and LGA will be registered. SGA and LGA are defined as birth weight below the 10th percentile, and above the 90th percentile of normal values for gestational age and gender, respectively.[66] The measurements in the child will include obtaining blood samples to determine glucose and insulin levels, and the lipid profile at birth (from cord blood) and at 12 months of age. Lung function at 6 weeks and 12 months postpartum in infants will be assessed by measurements of Functional Residual Capacity, Lung Clearance Index, Tidal Volume and airway resistance using the tremoFlo® C-100 Airwave Oscillometry System (THORASYS, Montreal, QC, Canada). All lung measurements will take place according to international standards.[67] Furthermore, it will be registered whether the child receives (exclusive) breastfeeding.

Sample collection

Samples of the microbial flora, placental tissue and breast milk will be collected and stored. During the past years, it has been indicated that obesity is related to microbial dysbiosis. Notably, studies indicated that during pregnancy, the developing foetal gut is primed by the maternal gut microbiota and intestinal permeability, particularly towards the later stages of

gestation.[68 69] In addition, a major determinant of the microbiota composition of new-borns is the mode of delivery. Vaginally-delivered infants harbour bacterial communities resembling those of the maternal vagina, whereas gut microbiota of caesarean section-delivered infants are enriched in maternal skin microbiota.[70 71] Therefore, we are interested in investigating the microbiota composition of mothers and children in our study and determine what the role of weight loss is herein. There are also indications that breast milk harbours a specific microbial community, however literature is scarce. Breast milk will also be stored for future metabolomics analysis. Placenta tissue is stored and might be used for RNA-sequencing analysis, microscopy-studies and epigenetics.[72-75]

Stool samples will be collected each 3 months and each trimester during pregnancy from mother and at 6 weeks and 12 months of age from the child, using two faeces tubes with a spoon attached to the lid (Sarstedt, Nürmbrecht, Germany). When sampled, the participants will be instructed to put the faeces tubes in a frozen cool transport container and to store this container in the freezer. Within one week, participants will take the container including the samples to the study site where the samples will be stored at -80°C until further analysis. Vaginal (of the mother) and oral (of mother and child) microbiome will be collected using a vaginal and throat swab, respectively. These swabs will be stored in transport buffer at -80°C

until further analysis. Microbiota profiles will be generated using DNA isolation.[76] Placental tissue will be collected and stored according to the procedure as described earlier.[77]. Quantitative DNA methylation analysis will be performed to explore epigenetic changes. Regions of interest will be determined at the moment analysis will be performed, to adhere to the most current literature among epigenetic changes.[78 79] Breast milk will be collected and stored as reported by Lipkie et al.,[80] in order to analyse the breast milk composition.

Cost-effectiveness analysis

Questionnaires will be used to collect information on care utilisation. To measure costs, a questionnaire is developed taken into account the various life phases of the women. Relevant costs to be identified include healthcare, patient and family costs, and costs outside the health care sector. To generate quality adjusted life years (QALYs), quality of life is measured by the validated questionnaire EQ-5D-5L.[81 82]

Incentives

Participants will receive parking and travel costs. In order to acknowledge women for their efforts, they will receive one reward per period (before, during and after pregnancy) and will match with the period such as a 3D ultrasound during pregnancy.

Public and Patient involvement

Before the start of the study, women of childbearing age were interviewed to identify facilitators and barriers to participate in a lifestyle intervention. This highly useful information was incorporated in the program to increase successful participation. Women are therefore involved in the overall design and set up of the lifestyle intervention. Besides, the intervention for each participating woman will be adapted to her needs, possibilities and social situation. In addition, the main results will be disseminated to trial participants and they are involved in the development of an appropriate method of dissemination. The women therefore have a central position in the intervention and are involved in every phase of the study.

Data management

The data will be collected by using electronic case record forms (MACRO, Elsevier B.V., Amsterdam, the Netherlands) that are adapted to the requirements of the current study. By using MACRO, the data collected are according to the FAIR (Findable, Accessible, Interoperable and Reusable) criteria.[83] Data will be securely stored for 15 years.

Statistical analysis plan

Data will be analysed using SPSS 24.0 for Windows (SPSS Incorporated, Chicago, IL, USA). Descriptive statistics will be performed to describe the baseline characteristics of the study population. Parametric data will be presented as means with standard deviations, non-parametric distributed variables as median with interquartile ranges. Since the design is a repeated-measurement RCT, linear mixed model techniques based on the intention-to-treat principle will be used to analyse the difference between intervention and control group with respect to primary and secondary outcome measurements. This technique corrects for within-subject correlation and deals with missing values at random. Survival analysis will be used to determine the hazard ratio for smoking cessation and time to pregnancy. Exploratory, paired sample t-tests will be used to test for change in exploratory outcomes. Analyses will be adjusted for the stratification factors overweight/obesity and smoking status. A p-value <0.05 will be considered statistically significant.

ETHICS AND DISSEMINATION

This study will be monitored independently by the Clinical Trial Centre Maastricht. All adverse events will be registered and reported to the medical ethics committee of Maastricht UMC+.

The knowledge derived from this study will be made available for the scientific community by publications in international peer reviewed scientific journals and will be presented at (inter)national scientific conferences. Study results will be relevant for both researchers as well as for primary care providers (including midwives, general practitioners, and youth health care workers) and secondary care providers (including gynaecologists, hospital-based midwives, and paediatricians). Furthermore, future study results will be presented and discussed with policy makers and the public domain.

The TOP-mums lifestyle intervention makes use of existing, regional initiatives (that are financially covered) for a sustainable solution for lifestyle improvement. Therefore, in case proven to be a successful intervention, the approach of TOP-mums can easily be extended to a broader area. A dissemination plan for regional and national implementation is developed.

DISCUSSION

The main goal of our RCT is to study the effects of a multidisciplinary lifestyle intervention for women who plan to conceive, and with overweight or obesity with consequently a high risk of perinatal morbidity. The TOP-mums study is one of the first RCT's that studies the effect of a preconceptionally started, multidisciplinary and personalised lifestyle intervention on different

behavioural, cardiovascular and perinatal outcomes of mother and child in the period before, during and after pregnancy. There is growing evidence that alterations in maternal metabolic and placental function occur during the first trimester of pregnancy, prior to when most interventions are started.[33 84] To guarantee healthy living from conception on, the lifestyle intervention in this study already starts preconceptionally.

Previous research regarding preconception lifestyle interventions is limited and especially the effectiveness of multidisciplinary and customised interventions is unclear.[85-87] The majority of the existing studies targeted subfertile women undergoing assisted reproductive technologies and discontinued the intervention once women became pregnant. When considering interpregnancy weight change, it has been shown that weight loss between pregnancies can reduce the incidence rates of perinatal complications.[26] This paves the way to execute an extensive effect evaluation of the lifestyle intervention in the current study. The study will significantly contribute to the elaboration of the knowledge on the effects of preconception lifestyle guidance on improving health for the current and next generations. One of the strengths of our study is that the lifestyle intervention is developed based on the experiences and wishes of the target group itself and is customised to the personal objectives and wishes.

Another asset of this study is the number of data collected, allowing us a better understanding of the consequences and intermediating factors of lifestyle on the health of mother and child.

In this study, most women who are willing to participate might be motivated to change their lifestyle. These women will be allocated to the control group as well, thereby leading to seek for additional lifestyle guidance in this group, potentially diluting the intervention effect. It is known that poor adherence and dropout is frequently experienced in lifestyle interventions. With the processes that are incorporated in the current lifestyle intervention, such as the customised approach and organising activities as much as possible in the direct neighbourhood of participants and at different time slots, the experience of our research group is that we can avoid dropout as much as possible.[88] It is possible that the data collection will be experienced as extensive by the participants. However, the extensive experience of our research group with other lifestyle interventions[89-91] is that participants appreciate monitoring of their health and participants will be motivated by that.

By improving lifestyle in the preconception phase the earliest origins of chronic diseases might be tackled. Therefore, the multidisciplinary and customised lifestyle intervention in the TOP-

mums study has the potential to benefit global public health by disrupting the vicious circle of transferring harmful lifestyle influences from generation to generation.

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AUTHOR CONTRIBUTIONS

Study concept and design: YT, KvdK, MS, ED, LZ, RST, BK and AV. *Acquisition of data*: YT and LK. *Draft of manuscript and statistical analysis*: YT, KvdK, LK and AV. *Revision of manuscript for important intellectual content*: MS, ED, RST, LZ and BK. All authors gave final approval for publication.

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COMPETING INTERESTS

From 2016 to April 2019, Régine P.M. Steegers-Theunissen was CSO of Slimmere Zorg BV.

Other authors declare no conflict of interest.

DATA SHARING STATEMENT

Data collected in this study will be available on reasonable request.

FIGURE LEGENDS

Figure 1: This vicious circle illustrates the intergenerational transmission of diseases. The TOP-mums study focuses on lifestyle improvement and the effects of this lifestyle improvement in the period between preconception and 1 year postpartum as illustrated in the upper part of the circle. The effects of an unhealthy lifestyle in this episode can impact health of the entire life span: a) longer time to conception and a higher risk of miscarriage; 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.

Figure 2: Flow chart of study procedures

REFERENCES

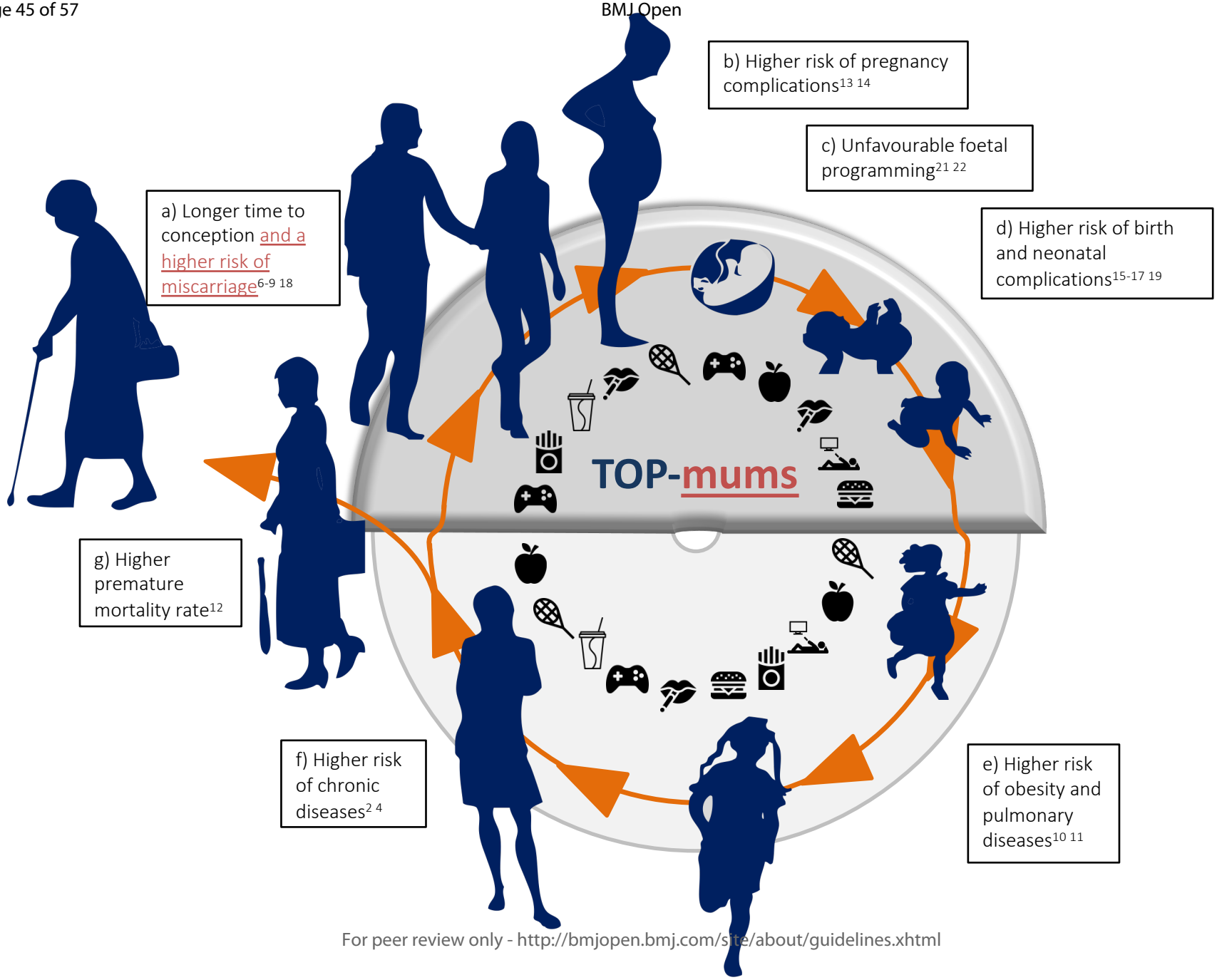
1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2197-223. doi: 10.1016/s0140-6736(12)61689-4I
2. Godfrey KM, Barker DJ. Fetal programming and adult health. *Public Health Nutr* 2001;4(2B):611-24.
3. Godfrey KM, Reynolds RM, Prescott SL, et al. Influence of maternal obesity on the long-term health of offspring. *The Lancet Diabetes & Endocrinology* 2017;5(1):53-64. doi: 10.1016/s2213-8587(16)30107-3I
4. Steegers-Theunissen RP, Twigt J, Pestinger V, et al. The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism. *Hum Reprod Update* 2013;19(6):640-55. doi: 10.1093/humupd/dmt041I
5. Gluckman PD, Hanson MA, Cooper C, et al. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 2008;359(1):61-73. doi: 10.1056/NEJMra0708473I
6. Brewer CJ, Balen AH. The adverse effects of obesity on conception and implantation. *Reproduction* 2010;140(3):347-64. doi: 10.1530/REP-09-0568I
7. Hassan MA, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. *Fertil Steril* 2004;81(2):384-92. doi: 10.1016/j.fertnstert.2003.06.027I
8. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. *Hum Reprod Update* 2007;13(3):209-23. doi: 10.1093/humupd/dml056I
9. Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. *Hum Reprod* 2004;19(7):1644-6. doi: 10.1093/humrep/deh277I
10. Scholtens S, Wijga AH, Brunekreef B, et al. Maternal overweight before pregnancy and asthma in offspring followed for 8 years. *Int J Obes* 2010;34(4):606-13. doi: 10.1038/ijo.2009.194I
11. Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2001;163(2):429-36. doi: 10.1164/ajrccm.163.2.2006009I
12. Di Angelantonio E, Bhupathiraju SN, Wormser D, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;388(10046):776-86. doi: 10.1016/S0140-6736(16)30175-1I
13. Scott-Pillai R, Spence D, Cardwell CR, et al. The impact of body mass index on maternal and neonatal outcomes: a retrospective study in a UK obstetric population, 2004-2011. *BJOG* 2013;120(8):932-9. doi: 10.1111/1471-0528.12193I
14. Voerman E, Santos S, Inskip H, et al. Association of Gestational Weight Gain With Adverse Maternal and Infant Outcomes. *JAMA* 2019;321(17):1702-15. doi: 10.1001/jama.2019.3820I
15. Liu P, Xu L, Wang Y, et al. Association between perinatal outcomes and maternal pre-pregnancy body mass index. *Obes Rev* 2016;17(11):1091-102. doi: 10.1111/obr.12455I
16. Stothard KJ, Tennant PW, Bell R, et al. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA* 2009;301(6):636-50. doi: 10.1001/jama.2009.113I
17. Ramachenderan J, Bradford J, McLean M. Maternal obesity and pregnancy complications: a review. *Aust N Z J Obstet Gynaecol* 2008;48(3):228-35. doi: 10.1111/j.1479-828X.2008.00860.xI
18. Hyland A, Piazza K, Hovey KM, et al. Associations between lifetime tobacco exposure with infertility and age at natural menopause: the Women's Health Initiative Observational Study. *Tob Control* 2016;25(6):706-14. doi: 10.1136/tobaccocontrol-2015-052510I

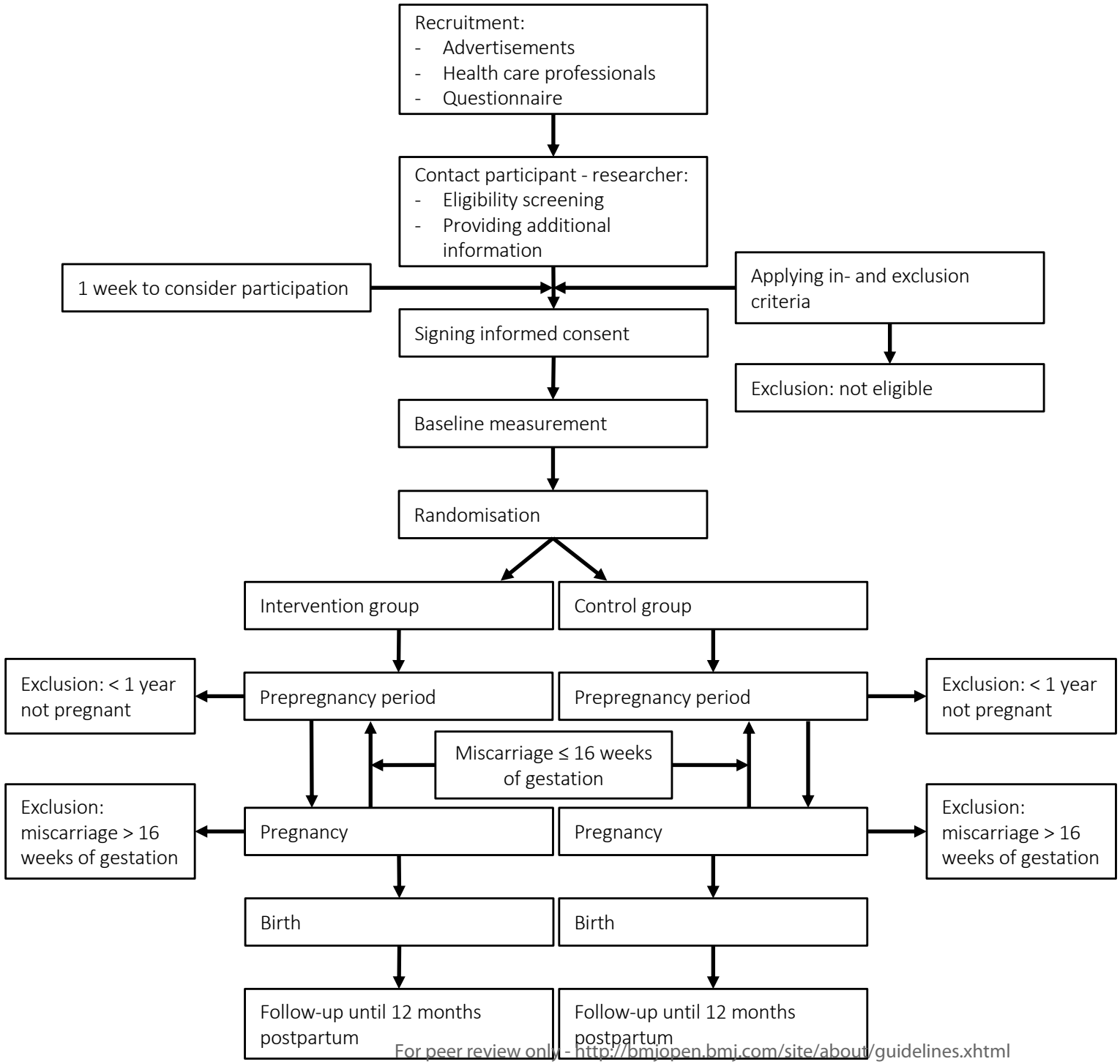
19. Ko TJ, Tsai LY, Chu LC, et al. Parental smoking during pregnancy and its association with low birth weight, small for gestational age, and preterm birth offspring: a birth cohort study. *Pediatr Neonatol* 2014;55(1):20-27. doi: 10.1016/j.pedneo.2013.05.005I
20. Eriksson JG, Sandboge S, Salonen MK, et al. Long-term consequences of maternal overweight in pregnancy on offspring later health: findings from the Helsinki Birth Cohort Study. *Ann Med* 2014;46(6):434-38. doi: 10.3109/07853890.2014.919728I
21. Burdge GC, Slater-Jefferies J, Torrens C, et al. Dietary protein restriction of pregnant rats in the F0 generation induces altered methylation of hepatic gene promoters in the adult male offspring in the F1 and F2 generations. *Br J Nutr* 2007;97(3):435-39. doi: 10.1017/s0007114507352392I
22. Gohir W, Ratcliffe EM, Sloboda DM. Of the bugs that shape us: maternal obesity, the gut microbiome, and long-term disease risk. *Pediatr Res* 2015;77(1-2):196-204. doi: 10.1038/pr.2014.169I
23. Nieuwdorp M, Gilijamse PW, Pai N, et al. Role of the microbiome in energy regulation and metabolism. *Gastroenterol* 2014;146(6):1525-33. doi: 10.1053/j.gastro.2014.02.008I
24. Backhed F, Roswall J, Peng Y, et al. Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. *Cell Host Microbe* 2015;17(5):690-703. doi: 10.1016/j.chom.2015.04.004I
25. i-WIP Collaborative group. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. *BMJ* 2017;358:j3119. doi: 10.1136/bmj.j3119I
26. Getahun D, Ananth CV, Peltier MR, et al. Changes in prepregnancy body mass index between the first and second pregnancies and risk of large-for-gestational-age birth. *Am J Obstet Gynecol* 2007;196(6):530 e1-e8. doi: 10.1016/j.ajog.2006.12.036I
27. Whiteman VE, Aliyu MH, August EM, et al. Changes in prepregnancy body mass index between pregnancies and risk of gestational and type 2 diabetes. *Arch Gynecol Obstet* 2011;284(1):235-40. doi: 10.1007/s00404-011-1917-7I
28. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi: 10.1136/bmj.e7586I
29. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC2013.
30. Statistics Netherlands. StatLine: Birth, key numbers fertility, maternal age, region [Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37201/table?ts=1561462862456 accessed 25-06-2019.
31. Mutsaerts MAQ, van Oers AM, Groen H, et al. Randomized Trial of a Lifestyle Program in Obese Infertile Women. *N Engl J Med* 2016;374(20):1942-53. doi: 10.1056/NEJMoa1505297I
32. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009;374(9702):1677-86. doi: 10.1016/S0140-6736(09)61457-4I
33. Thangaratinam S, Rogozinska E, Jolly K, et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. *BMJ* 2012;344:e2088. doi: 10.1136/bmj.e2088I
34. Vinter CA, Jensen DM, Ovesen P, et al. The LiP (Lifestyle in Pregnancy) study: a randomized controlled trial of lifestyle intervention in 360 obese pregnant women. *Diabetes Care* 2011;34(12):2502-07. doi: 10.2337/dc11-1150I
35. Althuizen E, van der Wijden CL, van Mechelen W, et al. The effect of a counselling intervention on weight changes during and after pregnancy: a randomised trial. *BJOG* 2013;120(1):92-99. doi: 10.1111/1471-0528.12014I
36. Hoeger KM, Kochman L, Wixom N, et al. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. *Fertil Steril* 2004;82(2):421-29. doi: 10.1016/j.fertnstert.2004.02.104I

37. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 2003;348(21):2082-90. doi: 10.1056/NEJMoa022207I
38. Simpson JL. Incidence and timing of pregnancy losses: relevance to evaluating safety of early prenatal diagnosis. *Am J Med Genet* 1990;35(2):165-73. doi: 10.1002/ajmg.1320350205I
39. Zhou H, Liu Y, Liu L, et al. Maternal pre-pregnancy risk factors for miscarriage from a prevention perspective: a cohort study in China. *Eur J Obstet Gynecol Reprod Biol* 2016;206:57-63. doi: 10.1016/j.ejogrb.2016.07.514I
40. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, et al. Subfecundity in overweight and obese couples. *Hum Reprod* 2007;22(6):1634-37. doi: 10.1093/humrep/dem035I
41. Hull MG, North K, Taylor H, et al. Delayed conception and active and passive smoking. The Avon Longitudinal Study of Pregnancy and Childhood Study Team. *Fertil Steril* 2000;74(4):725-33.
42. Nederlandse Vereniging voor Obstetrie en Gynaecologie. Landelijke netwerkrichtlijn Subfertiliteit 2010 [Available from: https://www.nvog.nl/wp-content/uploads/2018/02/Subfertiliteit-landelijke-netwerkrichtlijn-1.0-20-05-2011.pdf.
43. Miller WR, Rollnick S. Motivational Interviewing, Second Edition: Preparing People for Change: Guilford Publications 2002.
44. Burke BL, Arkowitz H, Menchola M. The efficacy of motivational interviewing: a meta-analysis of controlled clinical trials. *J Consult Clin Psychol* 2003;71(5):843-61. doi: 10.1037/0022-006x.71.5.843I
45. Van Dijk MR, Huijgen NA, Willemsen SP, et al. Impact of an mHealth Platform for Pregnancy on Nutrition and Lifestyle of the Reproductive Population: A Survey. *JMIR Mhealth Uhealth* 2016;4(2):e53. doi: 10.2196/mhealth.5197I
46. Van Dijk MR, Koster MP, Rosman AN, et al. Opportunities of mHealth in Preconception Care: Preferences and Experiences of Patients and Health Care Providers and Other Involved Professionals. *JMIR Mhealth Uhealth* 2017;5(8):e123. doi: 10.2196/mhealth.7834I
47. van Dijk MR, Koster MPH, Willemsen SP, et al. Healthy preconception nutrition and lifestyle using personalized mobile health coaching is associated with enhanced pregnancy chance. *Reprod Biomed Online* 2017;35(4):453-60. doi: 10.1016/j.rbmo.2017.06.014I
48. van Dijk MR, Oostingh EC, Koster MP, et al. The use of the mHealth program Smarter Pregnancy in preconception care: rationale, study design and data collection of a randomized controlled trial. *BMC Pregnancy Childbirth* 2017;17(1):46. doi: 10.1186/s12884-017-1228-5I
49. www.co-eur.com [
50. The Netherlands Nutrition Centre. De Schijf van Vijf [18-07-2018]. Available from: https://www.voedingscentrum.nl/nl/gezond-eten-met-de-schijf-van-vijf.aspx accessed 18-07-2018.
51. Institute of Medicine. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington (DC): National Academies Press (US) 2009.
52. Shiri R, Coggon D, Falah-Hassani K. Exercise for the prevention of low back and pelvic girdle pain in pregnancy: A meta-analysis of randomized controlled trials. *European Journal of Pain* 2018;22(1):19-27. doi: 10.1002/ejp.1096I
53. Westerterp KR, Wouters L, van Marken Lichtenbelt WD. The Maastricht protocol for the measurement of body composition and energy expenditure with labeled water. *Obes Res* 1995;3 Suppl 1:49-57.
54. Catalano PM, Wong WW, Drago NM, et al. Estimating body composition in late gestation: a new hydration constant for body density and total body water. *Am J Physiol* 1995;268(1 Pt 1):E153-8.
55. van Raaij JM, Peek ME, Vermaat-Miedema SH, et al. New equations for estimating body fat mass in pregnancy from body density or total body water. *Am J Clin Nutr* 1988;48(1):24-9.
56. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* 1982;36(5):936-42. doi: 10.1093/ajcn/36.5.936I

57. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J Psychosom Res* 1985;29(1):71-83.
58. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. *Lancet* 1998;351(9105):805-06. doi: 10.1016/S0140-6736(05)78933-9I
59. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28(7):412-19.
60. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol* 2014;63(7):636-46. doi: 10.1016/j.jacc.2013.09.063I
61. Ding J, Wai KL, McGeechan K, et al. Retinal vascular caliber and the development of hypertension: a meta-analysis of individual participant data. *J Hypertens* 2014;32(2):207-15. doi: 10.1097/HJH.0b013e32836586f4I
62. Nederlandse Vereniging voor Obstetrie en Gynaecologie. Richtlijn Diabetes mellitus en zwangerschap 2018 [Available from: https://www.nvog.nl/wp-content/uploads/2018/10/NVOG-richtlijn-Diabetes-mellitus-en-zwangerschap-v3.0-2018.pdf.
63. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications : report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus 1999 [Available from: https://apps.who.int/iris/handle/10665/66040.
64. Nederlandse Vereniging voor Obstetrie en Gynaecologie. Richtlijn Hypertensieve aandoeningen in de zwangerschap 2011 [Available from: https://richtlijnendatabase.nl/richtlijn/hypertensieve_aandoeningen_in_de_zwangerschap/hypertensieve_aandoeningen_-_startpagina.html.
65. Nederlandse Vereniging voor Obstetrie en Gynaecologie. Richtlijn Foetale groeirestrictie 2018 [Available from: https://www.nvog.nl/wp-content/uploads/2018/08/NVOG-richtlijn-FGR-2017-definitief-incl.-aanpassingen-Doppler-ACM-aug.-2018.pdf.
66. Visser GH, Eilers PH, Elferink-Stinkens PM, et al. New Dutch reference curves for birthweight by gestational age. *Early Hum Dev* 2009;85(12):737-44. doi: 10.1016/j.earlhumdev.2009.09.008I
67. Stocks J, Sly PD, Tepper RS, et al. Infant respiratory function testing. New York: Wiley-Liss 1996.
68. Kerr CA, Grice DM, Tran CD, et al. Early life events influence whole-of-life metabolic health via gut microflora and gut permeability. *Crit Rev Microbiol* 2015;41(3):326-40. doi: 10.3109/1040841x.2013.837863I
69. Koren O, Goodrich JK, Cullender TC, et al. Host remodeling of the gut microbiome and metabolic changes during pregnancy. *Cell* 2012;150(3):470-80. doi: 10.1016/j.cell.2012.07.008I
70. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A* 2010;107(26):11971-5. doi: 10.1073/pnas.1002601107I
71. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nat Med* 2016;22(3):250-3. doi: 10.1038/nm.4039I
72. Lundgren SN, Madan JC, Emond JA, et al. Maternal diet during pregnancy is related with the infant stool microbiome in a delivery mode-dependent manner. *Microbiome* 2018;6(1):109. doi: 10.1186/s40168-018-0490-8I
73. Galley JD, Bailey M, Kamp Dush C, et al. Maternal obesity is associated with alterations in the gut microbiome in toddlers. *PLoS One* 2014;9(11):e113026. doi: 10.1371/journal.pone.0113026I
74. Seganfredo FB, Blume CA, Moehlecke M, et al. Weight-loss interventions and gut microbiota changes in overweight and obese patients: a systematic review. *Obes Rev* 2017;18(8):832-51. doi: 10.1111/obr.12541I
75. Ley RE. Obesity and the human microbiome. *Curr Opin Gastroenterol* 2010;26(1):5-11. doi: 10.1097/MOG.0b013e328333d751I
76. Ivorra C, Fraga MF, Bayon GF, et al. DNA methylation patterns in newborns exposed to tobacco in utero. *J Transl Med* 2015;13:25. doi: 10.1186/s12967-015-0384-5I

77. Nelissen EC, Dumoulin JC, Busato F, et al. Altered gene expression in human placentas after IVF/ICSI. *Hum Reprod* 2014;29(12):2821-31. doi: 10.1093/humrep/deu241I
78. Sadr Dadres G, Whitaker KM, Haapala JL, et al. Relationship of Maternal Weight Status Before, During, and After Pregnancy with Breast Milk Hormone Concentrations. *Obesity (Silver Spring)* 2019;27(4):621-28. doi: 10.1002/oby.22409I
79. Kon IY, Shilina NM, Gmoshinskaya MV, et al. The Study of Breast Milk IGF-1, Leptin, Ghrelin and Adiponectin Levels as Possible Reasons of High Weight Gain in Breast-Fed Infants. *Annals of Nutrition and Metabolism* 2014;65(4):317-23. doi: 10.1159/000367998I
80. Lipkie TE, Morrow AL, Jouni ZE, et al. Longitudinal Survey of Carotenoids in Human Milk from Urban Cohorts in China, Mexico, and the USA. *PLoS One* 2015;10(6):e0127729. doi: 10.1371/journal.pone.0127729I
81. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-xI
82. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013;22(7):1717-27. doi: 10.1007/s11136-012-0322-4I
83. Wilkinson MD, Dumontier M, Aalbersberg IJ, et al. The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* 2016;3:160018. doi: 10.1038/sdata.2016.18I
84. Catalano P, deMouzon SH. Maternal obesity and metabolic risk to the offspring: why lifestyle interventions may have not achieved the desired outcomes. *Int J Obes* 2015;39(4):642-49. doi: 10.1038/ijo.2015.15I
85. Temel S, van Voorst SF, Jack BW, et al. Evidence-based preconceptional lifestyle interventions. *Epidemiol Rev* 2014;36:19-30. doi: 10.1093/epirev/mxt003I
86. Hillemeier MM, Downs DS, Feinberg ME, et al. Improving women's preconceptional health: findings from a randomized trial of the Strong Healthy Women intervention in the Central Pennsylvania women's health study. *Womens Health Issues* 2008;18(6 Suppl):S87-96. doi: 10.1016/j.whi.2008.07.008I
87. Lan L, Harrison CL, Misso M, et al. Systematic review and meta-analysis of the impact of preconception lifestyle interventions on fertility, obstetric, fetal, anthropometric and metabolic outcomes in men and women. *Hum Reprod* 2017;32(9):1925-40. doi: 10.1093/humrep/dex241I
88. Burgess E, Hassmen P, Pumpa KL. Determinants of adherence to lifestyle intervention in adults with obesity: a systematic review. *Clin Obes* 2017;7(3):123-35. doi: 10.1111/cob.12183I
89. Willeboordse M, van de Kant KDG, Tan FE, et al. A Multifactorial Weight Reduction Programme for Children with Overweight and Asthma: A Randomized Controlled Trial. *PLoS One* 2016;12(7):e0181130. doi: 10.1371/journal.pone.0157158I
90. Hutchinson SG, van Breukelen G, van Schayck CP, et al. Motivational interviewing and urine cotinine feedback to stop passive smoke exposure in children predisposed to asthma: a randomised controlled trial. *Sci Rep* 2017;7(1):15473. doi: 10.1038/s41598-017-15158-2I
91. Rijks JM, Plat J, Mensink RP, et al. Children With Morbid Obesity Benefit Equally as Children With Overweight and Obesity From an Ongoing Care Program. *J Clin Endocrinol Metab* 2015;100(9):3572-80. doi: 10.1210/jc.2015-1444I





SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 3
	2b	All items from the World Health Organization Trial Registration Data Set	Page 3
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	Page 20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, page 20
	5b	Name and contact information for the trial sponsor	Page 20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 5 & 6
	6b	Explanation for choice of comparators	Page 7
Objectives	7	Specific objectives or hypotheses	Page 7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 7 & 8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 18 & 19
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 12-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Not applicable
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Not applicable
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 18 & 19

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Not applicable
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not applicable

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	-
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page 16

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Informed consent form "TOP-mums, for a healthy start"

Child

I have been asked to consent to the following person/my child participating in this medical-scientific study.

Name of study subject (child): Date of birth: ____ / ____ / _____

- I have read the subject information form for the parents/guardians. I was able to ask questions. My questions have been answered to my satisfaction. I had enough time to decide whether I want my child to participate.
- I know that participation voluntary. I know that I may decide at any time that I do not want my child to participate after all or to withdraw from the study. I do not need to give a reason for this.
- I give permission for my child's general practitioner/treating specialist/youth health care division to be informed about my child's participation in this study.
- I know that some people may have access to all data of my child to verify the study. These people are listed in the information letter and the Brochure "Medical Research: General information for subjects". I consent to the inspection by them.
- I approve that my child's data will be used in order to achieve the goals as described in the information letter.
- I give permission for information to be requested from my child's youth health care division as described in the information letter.
- I approve that my child's data that will be collected during this study, will be stored for 15 years.
- I **do/do not*** consent to keeping my child's bodily material that will be collected during the study for 15 years after the end of this study. In the future, the bodily material may be used for research questions in line with this study.
- I **do/do not*** approve to be approached for further research.

* Please cross the option that is not applicable.

I agree to this person's/my child's participation in this study.

Name of the parent/legal guardian:

Signature: Date: ____ / ____ / _____

Name of the parent/legal guardian:

Signature: Date: ____ / ____ / _____

I declare that I have fully informed the abovementioned persons about the study referred to.

If information becomes available during the study that could affect the parent's or guardian's consent, I will notify him/her about this in good time.

Name of investigator (or his/her representative):

Signature: Date: ____ / ____ / _____

If applicable, additional information was given by:

Name:

Job title:

Signature: Date: ____ / ____ / _____

Informed consent form "TOP-mums, for a healthy start"

Women who plan to conceive

- I have read the subject information form. I was able to ask questions. My questions have been answered to my satisfaction. I had enough time to decide whether to participate.
- I know that participation is voluntary. I know that I may decide at any time not to participate after all or to withdraw from the study. I do not need to give a reason for this. When I decide to quit my participation, this will not have any influence on the usual care for me.
- I know that, when I decide to quit my participation, the researcher may ask me to complete questionnaires regarding expenditures in terms of my pregnancy and child.
- I give permission for my general practitioner, midwife and treating specialist to be informed that I am participating in this study.
- I agree that my general practitioner and/or treating specialist will be informed of coincidental findings that may be of interest for my health.
- I know that some people have access to all my data to verify the study. These people are listed in the information letter and the Brochure "Medical Research: General information for subjects". I consent to the inspection by them.
- I approve that my data will be used in order to achieve the goals as described in the information letter.
- In addition, I approve that my personal and medical information, as described in the information letter, will be retrieved from my midwife and/or my gynaecologist.
- I know that the researcher will approach me after my delivery, to ask for informed consent for participation of my child in the study.
- I approve that my data that will be collected during this study, will be stored for 15 years.
- I **do/do not*** approve to store my human tissue that will be collected during the study for 15 years after the end of this study. In the future, the human tissue may be used for research questions in line with this study.
- I **do/do not*** desire to be informed about the results of the study.
- I **do/do not*** approve to be approached for further research.

* Please cross the option that is not applicable.

I want to participate in this study.

Name of study subject:

Signature: Date: ____ / ____ / _____

I hereby declare that I have fully informed this study subject about this study.

If information comes to light during the course of the study, that could affect the study subject's consent, I will inform her of this in a timely fashion.

Name of investigator (or his/her representative):

Signature: Date: ____ / ____ / _____

If applicable, additional information was given by:

Name:

Job title:

Signature: Date: ____ / ____ / _____

Supplement 4: Consultations with personal lifestyle coach and dietician

	Preconception							During pregnancy								Postpartum						
	Baseline	1 month	2 months	3 months	6 months	9 months	12 months	6 weeks	12 weeks	16 weeks	20 weeks	28 weeks	32 weeks	36 weeks	38 weeks	1 month	3 months	4 months	6 months	7.5 months	9 months	12 months
Personal lifestyle coach	x	x	x	x	x	x	x	x	x	x	x		x	x		x	x		x		x	x
Dietician	x	x		x	x	x		x	x		x	x		x		x		x		x		

Supplement 5: Questions screening eating disorder

1. Are you unsatisfied about your eating habits?
2. Do you ever eat secretly?
3. Does your body weight have influence on your emotional feelings?
4. Do you think that eating plays an important role in your life?
5. Have you ever been afraid of losing control of your eating behavior?
6. Have you ever had binge eating?
7. Do you ever have feelings of shame or guilt when you have eaten?
8. Have you ever had trouble concentrating because you had to think about food?

BMJ Open

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

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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

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Word count: Abstract 358; Body 5581; Tables: 1. Figures 2.

ABSTRACT

Introduction: Periconception obesity is associated with a higher risk for adverse perinatal outcomes such as gestational diabetes mellitus (GDM), preeclampsia, large for gestational age (LGA), operative delivery and preterm birth. Lifestyle interventions during pregnancy have resulted in insufficient effects on reducing these perinatal complications. A few reasons for this disappointing effect can be suggested: 1) the time period during pregnancy for improvement of developmental circumstances is too short; 2) the periconception period in which complications originate is not included; and 3) lifestyle interventions may not have been sufficiently multidisciplinary and customised. A preconception lifestyle intervention might be more effective to reduce perinatal complications. Therefore, the aim of the TOP-mums study is to evaluate the effect of a lifestyle intervention starting prior to coneption on lifestyle behaviour change.

Methods and analysis: This protocol outlines a non-blinded, randomised controlled trial. One hundred and twelve women (18-40 years of age) with overweight or obesity (Body Mass Index (BMI) ≥25.0 kg/m^2) who plan to conceive within one year, will be randomised to either the intervention or 'care as usual' group. The intervention group will receive a multidisciplinary, customised lifestyle intervention stimulating physical activity, a healthy diet and smoking cessation, if applicable. The lifestyle intervention and monitoring will take place until 12 months

postpartum. The primary outcome is difference in weight in kg from baseline to 6 weeks postpartum. Secondary outcomes are gestational weight gain, postpartum weight retention, smoking cessation, dietary and physical activity habits. Furthermore, exploratory outcomes include body composition, cardiometabolic alterations, time to pregnancy, need for assisted reproductive technologies, perinatal complications of mother and child, and lung function of the child. Vaginal and oral swabs, samples of faeces, breast milk, placenta and cord blood will be stored for evaluation of microbial flora, epigenetic markers and breast milk composition. Furthermore, a cost-effectiveness analysis will take place.

Ethics and dissemination: Ethical approval was obtained from the Medical Ethical Committee of Maastricht University Medical Centre+ (NL52452.068.15/METC152026). Knowledge derived from this study will be made available by publications in international peer reviewed scientific journals and will be presented at (inter)national scientific conferences. A dissemination plan for regional and national implementation of the intervention is developed.

Trial registration number: ClinicalTrials.gov NCT02703753.

Keywords: Lifestyle, preconception, non-communicable diseases, pregnancy complications

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This randomised controlled trial is innovative by evaluating effects of a lifestyle intervention that starts prior to preconception and continues until one year postpartum;
- The strength of the intervention is it's multidisciplinary and personalised approach, taken into account the wishes, needs and opportunities of the women at risk;
- This study will collect a broad range of data, including longitudinal data regarding mechanisms hypothesised to be involved in the intergenerational transmission of diseases, which is scarcely studied yet and allows the generation of new hypotheses;
- Women who are willing to participate in the study are potentially more motivated to change their lifestyle, also when allocated to the 'care as usual' group;
- The sample size calculated to answer the primary research question may be relatively small in order to achieve sufficient power for the effect evaluation of some outcome measurements, which therefore should be seen as exploratory.

INTRODUCTION

Worldwide, the prevalence of chronic diseases such as cardiovascular diseases, dyslipidaemia and diabetes mellitus is increasing. The rising burden from these chronic diseases imposes new challenges for health care.[1] Key risk factors in the development of chronic diseases are lifestyle habits such as smoking, lack of physical activity, unhealthy diet and being overweight. As illustrated in Figure 1, there is increasing evidence suggesting that the detrimental effects of being exposed to a certain lifestyle originate from the periconceptional period.[2-5] By tackling its earliest origins, improving preconception lifestyle is hypothesised to benefit global public health by addressing the increasing problem of chronic diseases.

Overweight and obesity before and during pregnancy negatively impact fertility,[6-8] pregnancy and birth outcomes,[4 9] and increase the risk for the development of chronic disease for both mother and child.[10-12] During pregnancy, women who are overweight or obese are at increased risk to develop complications such as gestational hypertension (GH), preeclampsia and gestational diabetes mellitus (GDM), and are more often in need of an emergency caesarean delivery.[13 14] In addition, maternal obesity is associated with a higher risk for adverse perinatal outcomes such as congenital abnormalities, large for gestational age (LGA), and birth trauma

as consequence of shoulder dystocia.[15 16] Besides, neonates of women with obesity are more likely to be admitted to the neonatal intensive care unit.[17] In addition to overweight, it is clearly established that maternal smoking negatively affects the health of mother and new-born. Maternal smoking decreases fertility[18] and intra-uterine exposure to smoking is associated with a higher risk for small for gestational age (SGA) and preterm birth.[19]

The risk of adverse events among offspring can extend through adulthood, demonstrating a vicious circle of intergenerational transmission of diseases.[3 5 20] Several studies suggest that intra-uterine exposure to an unhealthy lifestyle can increase the risk of cardiovascular, metabolic and endocrine disease in adult life by unfavourable foetal programming.[2 5] Studies in animals indicate that epigenetic processes might be an important link between maternal lifestyle habits, and the risk for developing obesity and chronic diseases in adult offspring. Epigenetic processes modulate gene transcription, establishing a detrimental epigenome during embryogenesis and early development of the foetus.[21] Furthermore, recent research suggests a role for the microbiota in the intergenerational transmission of obesity.[22] Bacterial diversity is influenced by obesity and gestational weight gain.[23] It is hypothesised that the transfer of an obesogenic microbial flora from mother to child during birth contributes to the intergenerational transmission of diseases.[24]

In an attempt to prevent perinatal complications, previous studies investigated the effect of lifestyle behaviour modification during pregnancy. Although these interventions were successful in limiting gestational weight gain, they were unsuccessful in reducing GDM, preeclampsia and LGA in women with obesity.[25] It could be suggested that starting during pregnancy, the time span to achieve sufficient impact on pregnancy outcomes might be too short. In addition, most study protocols did not include a multidisciplinary and customised approach and did not take into account the effects of lifestyle during the periconception period in which perinatal complications often originate. Data from large population-based studies have shown that reducing BMI from overweight or obesity before the first pregnancy to normal weight before the subsequent pregnancy decreased the risk of GDM and LGA.[26 27] Therefore, a lifestyle intervention that starts during the preconception phase might be promising in reducing pregnancy and birth complications and thereby provide a more promising start for the future generation.

Aim

The primary aim of this study is to evaluate the impact of a preconception lifestyle intervention on weight change in women with overweight or obesity and with a child wish. Secondary study

aims are to evaluate the effect of the lifestyle intervention on gestational weight gain, postpartum weight retention and lifestyle habits such as physical activity, dietary intake and smoking behaviour. In addition, we will explore the effects of the intervention on cardiometabolic alterations, body composition, time to pregnancy, need for assisted reproductive technologies, and perinatal complications such as GDM, GH, preeclampsia, SGA, LGA and preterm birth, cardiometabolic alterations and lung function of the child. Furthermore, effects on the microbial flora, epigenetics and breast milk composition will be evaluated. Finally, a cost-effectiveness analysis of the lifestyle intervention will be conducted.

METHODS AND ANALYSIS

This protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement (see Supplement 1: SPIRIT checklist).[28] The TOP-mums study was approved by the Medical Ethical Committee of the Maastricht University Medical Centre+ (Maastricht UMC+; NL52452.068.15/METC152026).

Study design

This study is a randomised controlled trial (RCT) in which the participants and investigators will not be blinded due to pragmatic reasons. Participants will be randomised 1:1 in either the intervention or 'care as usual' group using block randomisation, with random block sizes of 2, 4 or 6. Randomisation will be stratified for overweight (BMI 25.0-29.9 kg/m^2), obesity (BMI ≥30.0 kg/m^2), and smoking status. The study will start before conception and will continue during pregnancy until one year after delivery. The lifestyle intervention and follow-up will end for women who are not pregnant within one year after randomisation and in case of a foetal demise between 16 and 24 weeks of gestational age (considered dropout). In case of a miscarriage before 16 weeks of gestational age, women will continue their participation in the study in order to follow-up a potential second pregnancy. Also for these women, the lifestyle intervention and follow-up will end when they are not pregnant within one year of initial randomisation.

After childbirth, both parents will be informed about participation of their child in the study both verbally as well as by the information letter. Participation of the child will only be feasible when both parents sign informed consent (see Supplement 2: Inform consent form child). When women/parents decide to quit participation, they will be asked to continue completing the cost

and quality of life questionnaires. This will enable us to perform an adequate as possible cost-effectiveness analysis. A flow chart of these procedures is presented in Figure 2.

Setting and study population

The study will be conducted in the South of Limburg, the Netherlands and is initiated and coordinated by Maastricht UMC+. Women will be eligible to participate in this study when meeting the following criteria: planning to conceive within one year, 18-40 years of age, and having a BMI ≥25.0 kg/m². Smoking is neither an inclusion nor an exclusion criterion. Only women who are able to read and speak Dutch or English will be included. Being treated in a fertility clinic is not an exclusion criterion. Women will be excluded when pregnant at the moment of randomisation. In addition, women will be excluded in case of haemodynamic significant heart disease, restrictive lung disease, congenital metabolic disease, diabetes type II dependent on medication, when intellectually disabled according to the DSM5 criteria,[29] or when they underwent bariatric surgery in the past.

Recruitment

Multiple recruitment strategies will be used to reach an adequate number of potential participants (see sample size). Recruitment will take place in the region of Maastricht, South

of Limburg, the Netherlands. In 2018, in this region 1,400 children were born.[30] Gynaecologists, midwives, general practitioners, and the Dutch youth health care system (a preventive health care system available for all children aged 0–19 years in the Netherlands) will be involved in recruiting women. At Maastricht UMC+, women may visit a gynaecologist for assisted reproductive technologies or may visit the preconception outpatient clinic because being at risk for developing pregnancy complications. In addition, women may visit their midwife with regard to the "child-wish consultation" or their general practitioner for removing or discussing their birth control. Women in the period between two pregnancies will also visit the Dutch youth health care system with their previous child(ren). In addition, subjects will be recruited via advertisements in local newspapers, magazines and websites for (expecting) young mothers, and via targeted social media campaigns for women of childbearing age living in the Maastricht area. Third, for another (cross-sectional) study (manuscript in preparation), women of reproductive age in the region received a questionnaire in which they would indicate whether they would be interested in participation in the current study. When inclusion criteria for the current study are met, these women will be contacted for participation.

Sample size

A sample size calculation was conducted for the primary outcome measure, defined as the mean difference in body weight in kg from baseline to 6 weeks postpartum. In a previous study that evaluated the effect of a lifestyle intervention in subfertile women, a mean reduction of 3.4 kg resulted in a higher natural conception rate.[31] Furthermore, 5-10% weight reduction was associated with a reduction of type 2 diabetes incidence in adults at risk due to a BMI ≥24.0 kg/m².[32] During pregnancy, lifestyle interventions resulted in 1.5 kg reduction in gestational weight gain.[33] In some studies, this weight reduction was associated with a lower prevalence of preeclampsia.[33] Taken into account these previous results, we determined a mean difference of 5±7 kg between the study groups as clinically relevant. For the sample size calculation, an alpha of 0.05 (two-sided) and a power of 80% is used. Taken into account a drop-out rate of 44% (based on drop-out rates of other lifestyle interventions (22%),[31 34-37] foetal demise after 16 weeks of gestation (1%),[38 39] and time to pregnancy >12 months (21%)[7 40 41]), a total of 110 subjects will be included in the current study.

Procedure

Subjects will be recruited via advertisements in newspapers, social media and via health care professionals (e.g. general practitioners, midwives, gynaecologists). Upon registration, women will be contacted by phone to test for eligibility based on inclusion and exclusion criteria, and

the patient information letter will be provided. One week of consideration to participate in the study will follow, before a baseline visit will be scheduled and informed consent will be obtained (Supplement 3). During the baseline visit, height and weight will be measured to confirm the inclusion criteria of BMI ≥25.0 kg/m². Based on BMI and smoking status, subjects will be allocated to either the intervention or 'care as usual' group by the online randomisation program ALEA (ALEA Clinical B.V., Abcoude, the Netherlands). Study visits will take place at Maastricht UMC+ and will take place during consultation with the personal lifestyle coach in order to minimise time investment. Within the scope of this study, health checks will be performed in addition to regular clinical practice, which might incidentally reveal aberrant findings. These findings will be discussed with the subject's primary care giver (e.g. general practitioner, midwife and/or gynaecologist) who will be responsible for adequate follow-up and/or treatment.

Care as usual

Both study groups will receive care as usual. In addition, women in the intervention group will receive the lifestyle intervention as described below. In the Netherlands, usual care for women before pregnancy includes access to the general practitioner and "child wish consultations" by a midwife. In addition, assisted reproductive technologies (ART) are part of care as usual for

subfertile women according to the Dutch infertility guidelines.[42] Access to ART will remain available during study participation. Pregnant women have access to their general practitioner and their midwife and/or gynaecologist. After pregnancy, maternity care in the first week postpartum at home will support breastfeeding. In addition, frequent consultations will take place at the youth health care division and for both mother and child access to the general practitioner is ensured. During these three periods, health care professionals will give lifestyle advices (according to national guidelines) when women specifically request for help regarding this topic or when health care professionals have other reasons for providing advice (e.g. when women have a cardiometabolic risk factor). In addition, health care professionals are not restricted to refer women to additional lifestyle guidance (e.g. by a dietician or lifestyle coach) when needed. Use of additional lifestyle guidance in the 'care as usual' group will be registered and taken into account in the effect evaluation.

Lifestyle intervention

The TOP-mums lifestyle intervention is a multidisciplinary intervention in which physical activity, a healthy diet, and if applicable, smoking cessation will be stimulated. The design of the study is based on a qualitative study executed by our research group to determine the needs and wishes of the women in the target population (results not published yet). This has

resulted in a personalised program, in which each participating woman will be assigned to her own personal lifestyle coach, who has a medical background and is trained in motivational interviewing.[43 44] On a regular basis, subjects will meet their coach (Supplement 4: Schedule consultations), who will develop a lifestyle program in concordance with each woman. To this end, lifestyle habits will be assessed by a nutritional diary, questionnaires and activity tracker at baseline. Based on this assessment, goals for improvements will be formulated. Dependent on the personal situation, participants may choose which goal to work on first, for which a combination of supporting programs is available (see below). The program will be offered in the periods before, during and after pregnancy, with specific lifestyle advice for each phase. This lifestyle intervention is easily accessible, innovative by the adaptive and proactive approach and the structured offer of lifestyle guidance.

Smarter pregnancy

Each woman will be provided with a free subscription to the mHealth coaching program 'Smarter Pregnancy' (Erasmus MC, University Medical Centre, Rotterdam, the Netherlands) that has been shown to improve nutrition and other lifestyle behaviours in this target population before.[45-48] The program offers personal coaching for 26 weeks, which is based on current personal circumstances, pregnancy, nutrition and lifestyle status. The tailored coaching

includes a maximum of three digital posts per week, providing advice, seasonal recipes for healthy meals and additional questions addressing lifestyle behaviour, taking into account pregnancy status.

Psychological guidance

For women who suffer from eating disorders in combination with overweight or obesity, psychological support can help with sustainable improvement of lifestyle. In order to determine the appropriate supporting programs that meet the wishes and needs of the women, a standardised quick-scan on eating habits (see Supplement 5: Screening eating disorders) will be used. A psychologist will assess the results and when an eating disorder is suspected, women will meet a psychologist of Co-eur who applies the DSM-5 criteria for comfirmation.[29] Co-eur is a mental health care institution specialised in the treatment of obesity in combination with eating disorders, in which a team of psychologists, dieticians and physiotherapists is involved in the treatment program.[49] The cornerstone of this program is targeting both the eating disorder and possible underlying psychological comorbidities (e.g. depression). Moreover, a sustainable change of lifestyle, and improvements of social and labour participation will be targeted. Cognitive behaviour therapy, cue exposure and system therapy

are techniques that will be used. In general, this involves coaching sessions two to three times a week, for four months.

Dietary guidance

A trained dietician will provide individual dietary advice every one or two months, according to the recommendations of the Netherlands Nutrition Centre.[50] to the main focus is targeting a healthy diet by improving dairy, fruit and vegetable intake, and decreasing the intake of low-nutritional, energy-dense foods. During pregnancy, a target for the maximum gestational weight gain will be set, according to the Institute of Medicine guidelines.[51] In the postpartum period, dietary advice for both mother and child will be provided. Breastfeeding will be encouraged by a trained lactation consultant. The frequency of dietician appointments is not fixed and can be adapted to the wishes and needs of the women, but a general guideline is provided in Supplement 4.

Physical activity

To support weekly physical activity at moderate intensity, a physical activity program conducted by professionals trained in physical education will be offered by the sports department of the municipality of Maastricht. In the preconception period, the physical activity

program will focus on improving aerobic capacity, muscle strengthening and increasing energy expenditure. The variable activities will take place at different times and locations to facilitate participation. During pregnancy, sessions will be conducted by a physiotherapist who is trained in offering a sports program for pregnant women (ZwangerFit®). Physical fitness, muscle strengthening, coordination and stabilisation, especially for the pelvic muscles are hallmark of this training. It is previously shown that pregnancy specific exercises reduce the risk of lower back pain, and sick leave because of lumbopelvic pain during pregnancy.[52] Starting at 6 weeks postpartum, up to 9 months postpartum, a paediatric physiotherapist will provide individual training sessions with a focus on emotional bonding, fun in playing for mother and baby and stimulating motor development of the child. These sessions will take place in the home environment. in addition, the paediatric physiotherapist will discuss participation in other activities such as baby swimming classes or baby mindfulness.

Smoking cessation

To target smoking cessation, the personal lifestyle coach will apply motivational interviewing techniques to support women to quit smoking. If necessary, women can be referred to a specialised smoking cessation coach for more extensive guidance.

Outcomes

To determine the effects of the lifestyle intervention on the health of the women and child, anthropometric, cardiometabolic, lifestyle habits, perinatal and postpartum outcomes will be measured and registered. In addition, blood, faecal, urine and breast milk samples will be collected according to the scheme as presented in Table 1.

The first step in determining what the effect is of the lifestyle intervention proposed in this study, is to examine the effect of the intervention on lifestyle behaviour change. It is assumed that lifestyle behaviour change results in weight change which is an objective outcome measurement. Based on the hypothesis that weight change will result in cardiometabolic changes, the next step is to study whether weight change has influence on secondary and exploratory outcomes.

Table 1: Overview of the measurements at different time points during the study

		Preconception						Pregnancy							Postpartum				
	Baseline	*1 month*	*2 months*	*3 months*	*6 months*	*9 months*	*12 months*	*6 weeks*	*12 weeks*	*20 weeks*	*26 weeks*	*32 weeks*	*36 weeks*	*40 weeks*	*Birth*	*6 weeks*	*3 months*	*6 months*	*9 months*	*12 months*
Anthropometric measurements																			
Weight, BMI, waist and hip circumference mother	x	x	x	x	x	x	x	x	x	x		x	x	x		x	x	x	x	x
Body composition mother	x											x						x		
Weight, height and BMI child																x	x	x	x	x
Cardiometabolic outcomes																			

Blood pressure mother	x	x	x	x	x	x	x	x	x	x		x	x	x		x	x	x	x	x
Pulse wave velocity mother	x			x	x		x	x		x		x						x		x
Retinal image mother	x			x	x		x	x		x		x						x		x
Glucose, insulin levels, lipid profile, liver enzymes mother				x				x		x		x					x	x		x
OGTT mother	x										x									x
Glucose, insulin levels, lipid profile child (cord blood)															x					
Glucose, insulin, lipid profile child																				x
Lifestyle habits																				
Accelerometer mother	x			x			x	x				x					x			x
Baecke questionnaire mother	x			x			x	x				x					x			x
Nutrition diary mother	x			x			x	x				x					x			x
Three Factor Eating Questionnaire mother	x			x			x	x				x					x			x
Vitamin D mother	x											x								
Smoking behaviour questionnaire mother	x	x	x	x	x	x	x	x	x	x		x	x	x		x	x	x	x	x
CO measurement mother	x	x	x	x	x	x	x	x	x	x		x	x	x		x	x	x	x	x
Urine cotinin mother	x			x				x		x		x				x				x
Feeding pattern child																x	x	x	x	x
Perinatal outcomes																				
Time to pregnancy								x												
Need for assisted reproductive technologies								x												
Miscarriage										x										
Pregnancy complications (GDM, GH, preeclampsia, IUGR)												x	x	x						
Method of delivery															x					
Induction of labour															x					
Postpartum measurements																				
Birth weight															x					
Gestational age															x					
APGAR-score															x					
Stillbirth															x					

Sample collection																			
Microbiome sampling mother	x			x	x	x	x	x		x		x					x	x	x	x
Epigenetic sampling															x					
Breast milk sampling																x				
Microbiome sampling child																x				x
Cost-effectiveness analysis																				
Cost questionnaire	x			x	x	x	x	x		x		x					x	x	x	x
EO-5D-5L	x			x	x	x	x	x		x		x					x	x	x	x

When women become pregnant at a certain time point before completing all preconception measurements, the remaining preconception measurements will be cancelled. Women will continue with measurements in the pregnancy period accordingly. The same procedure will take place when women give birth before 40 weeks of gestational age. Abbreviations: BMI, body mass index; CO, carbon monoxide; EQ-5D-5L, quality of life measurement; GDM, gestational diabetes mellitus; GH, gestational hypertension; IUGR, intrauterine growth restriction; OGTT, oral glucose tolerance test.

Anthropometric measurements

Body weight will be assessed in underwear with no shoes in kg to the nearest 0.1 kg using a medical calibrated weight scale (Model 799, seca gmbh & co. kg., Chino, USA), at each study visit. Height will be determined by a stadiometer (Model 220, seca gmbh & co. kg., Chino, USA) calibrated in 0.1 cm intervals. BMI will be calculated as the weight in kg divided by height in meters squared. Gestational weight gain is defined as weight in kg from 6 weeks of pregnancy to the last prenatal study visit and will be compared to the Institute of Medicine guidelines.[51] Postpartum weight retention is defined as the difference in weight in kg between 6 weeks of gestational age and 6 months postpartum.

Waist and hip circumferences will be measured with a non-elastic tape at the end of a natural breath at midpoint between the top of the iliac crest and the lower margin of the last palpable rib and at the widest point of the hip, respectively, standing on both feet equally with arms hanging down. The waist/hip ratio will be calculated. Furthermore, the body composition (i.e. fat and fat-free mass) will be measured at three time points during the study using deuterium dilution as described before.[53] During pregnancy, calculations for fat mass and fat-free mass will adjusted for gestational specific fat-free mass in which deuterium is distrusted as well.[54 55]

Lifestyle habits

To objectively measure physical activity level, participants will wear an accelerometer (ActiGraph, model wGT3X-BT, Pensacola, FL, USA) for seven days. Furthermore, the validated Baecke questionnaire will be used to measure work, sport and leisure activities.[56] To register dietary habits, women will be asked to complete a seven day nutritional diary. In addition, the validated Three Factor Eating Questionnaire (TFEQ) will be used to assess three aspects of eating behaviour: cognitive restraint, disinhibition, and hunger.[57] As a component of the nutritional assessment, serum 25-hydroxyvitamin D will be measured using the Immulite-1000. Vitamin D insufficiency is defined as < 50 nmol/L.[58] Smoking habits will be assessed by a questionnaire focussing on smoking behaviour, quitting history, the intention to quit, nicotine

dependence and self-efficacy. Biochemical verification of tobacco will be assessed through the piCO^{babyTM} carbon monoxide (CO) monitor (Bedfont® Scientific Ltd., Harrietsham, Maidstone, Kent) by measuring CO in exhaled breath. Long-term use of tobacco will be measured by the assessment of cotinin in urine.

Cardiometabolic outcomes

Fasting blood samples will be taken at different time points before, during and after pregnancy to determine blood glucose and insulin levels, lipid profile and liver enzymes (Table 1). Fasting plasma glucose will be determined using the Cobas 8000 modular analyser (F. Hoffmann-La Roche Ltd., Basel, Swiss) and serum insulin concentrations using the Immulite-1000 (Siemens Healthcare Diagnostics, Erlangen, Germany). Accordingly, the homeostatic model assessment of insulin resistance (HOMA-IR) will be calculated (fasting glucose (mmol/L)*(fasting insulin (µU/L)/22.5)).[59] All participants will undergo an oral glucose tolerance test (OGTT) at baseline, 26 weeks of gestational age, and 12 months postpartum. Blood glucose and insulin concentrations will be measured 1 and 2 hours after ingestion of 75g glucose. Fasting serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, free fatty acids (FFA), serum alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), and

alkaline phosphatase (ALP) concentrations, will be determined using the Cobas 8000 modular analyser.

Cardiovascular alterations will be measured by systolic and diastolic blood pressure (SBP and DBP), using a validated automatic device (A&D Medical UA-789XL, Saitama, Japan) on the left arm after 5-10 minutes rest in a sitting position for four times, with one minute rest in between. Mean SBP and DBP of the three last measurements will be calculated. Although cardiovascular morbidity such as a high blood pressure might not be present in women participating in the study (yet), 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,[60 61] these measurements are included in this study. Arterial stiffness will be assessed by the carotid-femoral and carotid-radial pulse wave velocity and Augmentation Index using the SphygmoCor device, model EM3 (ArtCor, Sydney, Australia). Further, retinal vascular images will be made of the right eye using a retina camera (Topcon TRC-NW-300, Topcon Corporation, Tokyo, Japan). The images will be analysed to measure the diameter of the four largest retinal arterioles and venules and to calculate the arteriovenous ratio.

Perinatal outcomes

Time to pregnancy is defined as the period between having the explicit wish to become pregnant to the moment of conception. The need for assisted reproductive technologies and the reason for this (e.g. chronic anovulation, not able to conceive for >12 months despite an ovulatory cycle) will be registered. Miscarriage, GDM, GH, preeclampsia, intrauterine growth restriction (IUGR), operative delivery, induction of labour, preterm birth, stillbirth, and congenital malformations will be registered after verifying medical records. Miscarriage is defined as the loss of the foetus before 16 weeks of gestation. Stillbirth is defined as intra-uterine foetal death after 16 weeks of gestation. GDM, GH, preeclampsia and IUGR will be determined according to the guidelines of the Dutch Society of Obstetrics and Gynaecology. GDM is defined as a diagnosis of hyperglycaemia during pregnancy, in a woman without pre-existing diabetes mellitus. The Dutch national guideline is in line with the World Health Organization guideline on Diagnosis and Classification of Diabetes Mellitus, which defined hyperglycaemia as the presence of either a fasting plasma glucose ≥7.0 mmol/l or 2-hour plasma glucose ≥7.8 mmol/l following a 75g OGTT.[62 63] GH is defined as systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least 90 mmHg after 20 weeks of gestational age.[64] Preeclampsia is defined as GH accompanied by proteinuria (at least 300 mg protein in a 24-hour urine collection).[64] IUGR is defined as estimated foetal weight

<p10, abdominal circumference <p10 or a decrease in growth of at least 20 percentiles within a minimal time frame of two weeks.[65] Preterm birth is defined as birth before 37 weeks of gestation and will subdivided in spontaneous (delivery started by primary contractions or spontaneous rupture of membranes) and indicated (including the performance of a caesarean delivery before onset of labour or induction of labour) preterm birth. Perinatal outcomes will be derived from hospital birth registries.

Postpartum measurements

Birth weight, APGAR-score 1 and 5 minutes after birth, SGA, and LGA will be derived from birth registries. SGA and LGA are defined as birth weight below the 10th percentile, and above the 90th percentile of normal values for gestational age and gender, respectively.[66] Growth charts from the first year of life will be derived from regular Youth Health Care visits that are part of the Dutch health care system. Cord blood samples at birth and plasma at one year of age will be collected to determine glucose, insulin and lipid profile. Infant lung function will be assessed by measurements of Functional Residual Capacity, Lung Clearance Index, Tidal Volume and airway resistance using the tremoFlo® C-100 Airwave Oscillometry System (THORASYS, Montreal, QC, Canada) at 6 weeks and 12 months postpartum, according to

international standards.[67] Furthermore, feeding practices will be registered in terms of formula or (exclusive) breastfeeding.

Sample collection

During the past years, it has been indicated that obesity is related to microbial dysbiosis.[68-71] Notably, studies indicated that during pregnancy, the developing foetal gut is primed by the gut microbiota and intestinal permeability of the mother, particularly towards the later stages of gestation.[72 73] In addition, a major determinant of the microbiota composition of new-borns is the mode of delivery. Vaginally-delivered infants harbour bacterial communities resembling those of the maternal vagina, whereas the gut microbiota of caesarean section-delivered infants are enriched in maternal skin microbiota.[74 75] There are also indications that breast milk harbours a specific microbial community, however literature is scarce. Therefore, we aim to determine the microbiota composition of mothers and children (faecal, oral, vaginal, breast milk) and determine the role of weight loss herein. In addition, breast milk composition/metabolome will be investigated,[76 77] and placenta tissue will be collected for RNA-sequencing analysis, histology and epigenetics.

Faeces will be collected at home using the TagHemi collection system (TagHemi, Zeijen, The Netherlands), and divided over 2 sterile tubes at home (Sarstedt, Nürmbrecht, Germany). Subjects will be instructed to freeze their samples immediately after defecation and use a cool transport container for transport to the university. Within one week, participants will take the samples to the university for storage at -80°C until further analysis. Stool samples will be collected at baseline, which will be repeated every 3 months for the scope of the study, including each trimester of pregnancy. Child faecal samples will be collected at age 6 weeks and 12 months. Vaginal (of the mother) and oral (of mother and child) swabs will be stored in transport buffer at -80°C until further analysis. Breast milk will be collected and stored as reported by Lipkie et al.[78] Placental tissue will be collected and stored as described before.[79] Microbiota profiles will be generated. Quantitative DNA methylation analysis will be performed to explore epigenetic changes. Regions of interest will be determined at the moment analyses will be performed, to adhere to the most current literature among epigenetic changes.

Cost-effectiveness analysis

Questionnaires will be used to obtain insight in care utilisation. To determine costs (i.e. regarding healthcare, patient and family costs, and costs outside the healthcare sector), a questionnaire is developed taking into account the stage women are in (preconception,

pregnant, postpartum). . To generate quality adjusted life years (QALYs), quality of life is measured by the validated EQ-5D-5L questionnaire.[80 81]

Incentives

Parking and travel costs will be reimbursed. In order to acknowledge women for their efforts, during each study period (preconception, pregnancy, postpartum) an incentive is included such as a free 3D ultrasound during pregnancy.

Public and Patient involvement

To increase adherence, women in the target population were involved in the overall design of the current study. A large group of women of childbearing age was interviewed to identify facilitators and barriers to participate in a lifestyle intervention that were incorporated in the current protocol. In addition, the intervention for each participating woman will be adapted to her personal needs, possibilities and social situation. Main results will be disseminated to trial participants and they are involved in the development of an appropriate method of dissemination. Therefore, participating women have a central position in the intervention and are involved in every phase of the study.

Data management

Data will be collected using electronic case record forms (MACRO, Elsevier B.V., Amsterdam, the Netherlands) that were adapted to the requirements of the current study. By using MACRO, the data collected are according to the FAIR criteria (Findable, Accessible, Interoperable and Reusable).[82] Data will be securely stored for 15 years.

Statistical analysis plan

Data will be analysed using SPSS 24.0 for Windows (SPSS Incorporated, Chicago, IL, USA). Descriptive statistics will be performed for baseline characteristics of the study population. Parametric data will be presented as means with standard deviations, non-parametric distributed variables as median with interquartile ranges. Since the design is a repeated-measures RCT, linear mixed model techniques based on the intention-to-treat principle will be used to analyse the difference between intervention and 'care as usual' group with respect to primary and secondary outcome measurements. This technique corrects for within-subject correlation and deals with missing values at random. Survival analysis will be used to determine the hazard ratio for smoking cessation and time to pregnancy. Exploratory, paired sample t-tests will be used to test for change in exploratory outcomes. Analyses will be

adjusted for the stratification factors overweight/obesity and smoking status. A p-value <0.05 will be considered statistically significant.

ETHICS AND DISSEMINATION

This study will be monitored independently by the Clinical Trial Centre Maastricht. All adverse events will be registered and reported to the medical ethics committee of Maastricht UMC+.

The knowledge derived from this study will be made available for the scientific community by publications in international peer reviewed scientific journals and will be presented at (inter)national scientific conferences. Study results will be relevant for both researchers as well as for primary care providers (i.e. midwives, general practitioners, and youth health care workers) and secondary care providers (i.e. gynaecologists, hospital-based midwives, and paediatricians). Furthermore, study results will be presented and discussed with policy makers and the public domain.

The TOP-mums lifestyle intervention makes use of existing, regional initiatives (that are financially covered) for a sustainable solution for lifestyle improvement. Therefore, in case

proven to be a successful intervention, the approach of TOP-mums can easily be extended to a broader area. A dissemination plan for regional and national implementation is developed.

DISCUSSION

The main goal of our RCT is to study the effects of a multidisciplinary lifestyle intervention for women who plan to conceive, who are at higher risk for perinatal morbidity because of overweight or obesity. The TOP-mums study is one of the first studies that investigates the effect of a multidisciplinary and personalised lifestyle intervention starting in the preconception phase, on different behavioural, cardiovascular and perinatal outcomes of both mother and child before, during and after pregnancy. There is growing evidence that lifestyle-related aberrations of maternal metabolic health and placenta function occur during the first trimester of pregnancy, prior to when most interventions are started.[33 83] To foster healthy living from conception on, the lifestyle intervention in this study is initiated prior to conception.

Previous research regarding preconception lifestyle interventions is limited and the effectiveness of multidisciplinary and customised interventions is unclear.[84-86] The majority of existing studies targeted subfertile women undergoing assisted reproductive technologies and discontinued the intervention once women became pregnant. When considering

interpregnancy weight change, it has been shown that weight loss between pregnancies can reduce the incidence rates of perinatal complications.[26] This paves the way to execute an extensive effect evaluation of the lifestyle intervention in the current study. The study will significantly contribute to the elaboration of the knowledge on the effects of preconception lifestyle guidance on improving health for the current and next generations. One of the strengths of our study is that the lifestyle intervention is developed based on the experiences and wishes of the target group itself and is customised to the personal objectives of each participant. Another asset of this study is the amount of data collected, allowing us to better understand of the consequences and intermediating factors of lifestyle on the health of mother and child.

The current protocol has some limitations. First, most subjects might enter the study based on intrinsic motivation to implement lifestyle changes. This might result in the search for additional lifestyle guidance, also when allocated to the 'care as usual' group, thereby potentially diluting the intervention effect. Secondly, although pregnancy can be seen as a 'teachable moment', poor adherence and high dropout rates are frequently reported for this type of lifestyle interventions.[87] However, based on experience of our research group, we expect that the design of the current lifestyle intervention, including a customised approach and the

organisation of activities in proximity of subject's home and at different time points, will limit dropout rates.[88] It is possible that additional measurements for data collection might be experienced as extensive by the participants. However, the long-standing experience of our research group with other lifestyle interventions[89-91] is that participants mostly appreciate monitoring of their health, which in addition often increases motivation.

To conclude, the current TOP-mums protocol describes a personalised lifestyle intervention starting in preparation of conception, continuing until one year after birth. By improving lifestyle already in the preconception phase, the earliest origins of chronic disease might be tackled, thereby disrupting the vicious circle of transferring harmful lifestyle influences from generation to generation. The outcomes of the current multidisciplinary, customised lifestyle intervention might provide valuable information for public health initiatives to foster a healthy start for our next generation.

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AUTHOR CONTRIBUTIONS

Study concept and design: YT, KvdK, MS, ED, LZ, RST, BK and AV. *Acquisition of data*: YT and LK. *Draft of manuscript and statistical analysis*: YT, KvdK, LK and AV. *Revision content of manuscript:* YT, DR, KvdK MS, ED, RST, LZ, BK and AV. All authors read and approved the manuscript for final publication. AV has the primary responsibility for the final content.

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COMPETING INTERESTS

Régine P.M. Steegers Theunissen is initiator and developer of Smarter Pregnancy and does not have a commercial interest. The department of Obstetrics and Gynaecology of the Erasmus MC, University Medical Centre in Rotterdam is owner of this mHealth coaching tool. Other authors declare no conflict of interest.

DATA SHARING STATEMENT

Data collected in this study will be available on reasonable request.

FIGURE LEGENDS

Figure 1: This vicious circle illustrates the intergenerational transmission of disease. The TOP-mums study focuses on lifestyle improvement and the effects of this lifestyle improvement in the period between preconception and 1 year postpartum as illustrated in the upper part of the circle. The effects of an unhealthy lifestyle in this period can impact health of the entire life span: a) longer time to conception and a higher risk for miscarriage; b) higher risk for 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 for 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 for developing obesity and pulmonary diseases such as wheezing and asthmatic disease; f) higher risk for chronic diseases such as diabetes mellitus type 2, cardiovascular diseases and dyslipidaemia; g) higher premature mortality rate.

Figure 2: Flow chart of study procedures

REFERENCES

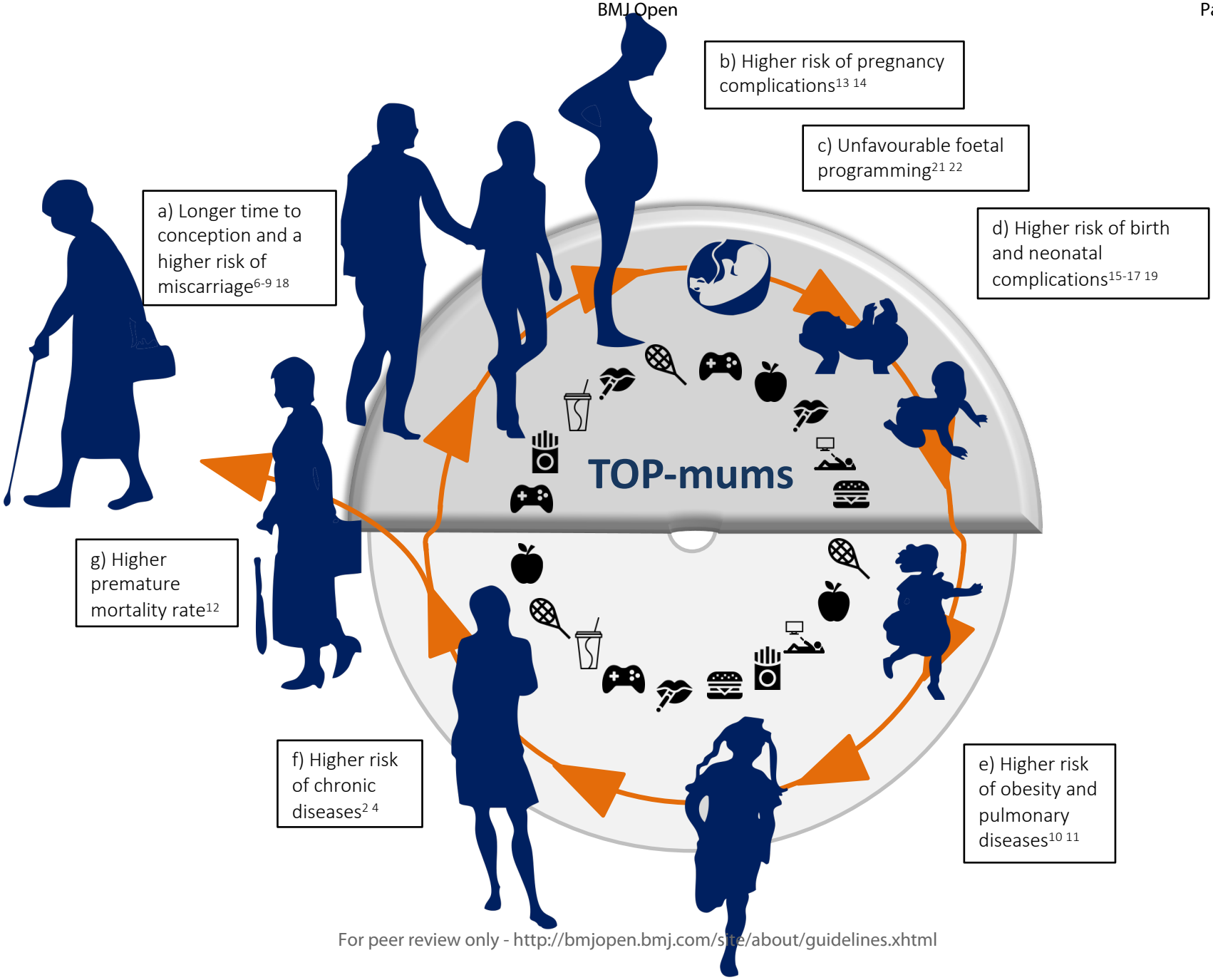
1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2197-223. doi: 10.1016/s0140-6736(12)61689-4I
2. Godfrey KM, Barker DJ. Fetal programming and adult health. *Public Health Nutr* 2001;4(2B):611-24.
3. Godfrey KM, Reynolds RM, Prescott SL, et al. Influence of maternal obesity on the long-term health of offspring. *The Lancet Diabetes & Endocrinology* 2017;5(1):53-64. doi: 10.1016/s2213-8587(16)30107-3I
4. Steegers-Theunissen RP, Twigt J, Pestinger V, et al. The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism. *Hum Reprod Update* 2013;19(6):640-55. doi: 10.1093/humupd/dmt041I
5. Gluckman PD, Hanson MA, Cooper C, et al. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 2008;359(1):61-73. doi: 10.1056/NEJMra0708473I
6. Brewer CJ, Balen AH. The adverse effects of obesity on conception and implantation. *Reproduction* 2010;140(3):347-64. doi: 10.1530/rep-09-0568I
7. Hassan MA, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. *Fertil Steril* 2004;81(2):384-92. doi: 10.1016/j.fertnstert.2003.06.027I
8. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. *Hum Reprod Update* 2007;13(3):209-23. doi: 10.1093/humupd/dml056I
9. Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. *Hum Reprod* 2004;19(7):1644-6. doi: 10.1093/humrep/deh277I
10. Scholtens S, Wijga AH, Brunekreef B, et al. Maternal overweight before pregnancy and asthma in offspring followed for 8 years. *Int J Obes* 2010;34(4):606-13. doi: 10.1038/ijo.2009.194I
11. Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2001;163(2):429-36. doi: 10.1164/ajrccm.163.2.2006009I
12. Di Angelantonio E, Bhupathiraju SN, Wormser D, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;388(10046):776-86. doi: 10.1016/S0140-6736(16)30175-1I
13. Scott-Pillai R, Spence D, Cardwell CR, et al. The impact of body mass index on maternal and neonatal outcomes: a retrospective study in a UK obstetric population, 2004-2011. *BJOG* 2013;120(8):932-9. doi: 10.1111/1471-0528.12193I
14. Voerman E, Santos S, Inskip H, et al. Association of Gestational Weight Gain With Adverse Maternal and Infant Outcomes. *JAMA* 2019;321(17):1702-15. doi: 10.1001/jama.2019.3820I
15. Liu P, Xu L, Wang Y, et al. Association between perinatal outcomes and maternal pre-pregnancy body mass index. *Obes Rev* 2016;17(11):1091-102. doi: 10.1111/obr.12455I
16. Stothard KJ, Tennant PW, Bell R, et al. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA* 2009;301(6):636-50. doi: 10.1001/jama.2009.113I
17. Ramachenderan J, Bradford J, McLean M. Maternal obesity and pregnancy complications: a review. *Aust N Z J Obstet Gynaecol* 2008;48(3):228-35. doi: 10.1111/j.1479-828X.2008.00860.xI
18. Hyland A, Piazza K, Hovey KM, et al. Associations between lifetime tobacco exposure with infertility and age at natural menopause: the Women's Health Initiative Observational Study. *Tob Control* 2016;25(6):706-14. doi: 10.1136/tobaccocontrol-2015-052510I

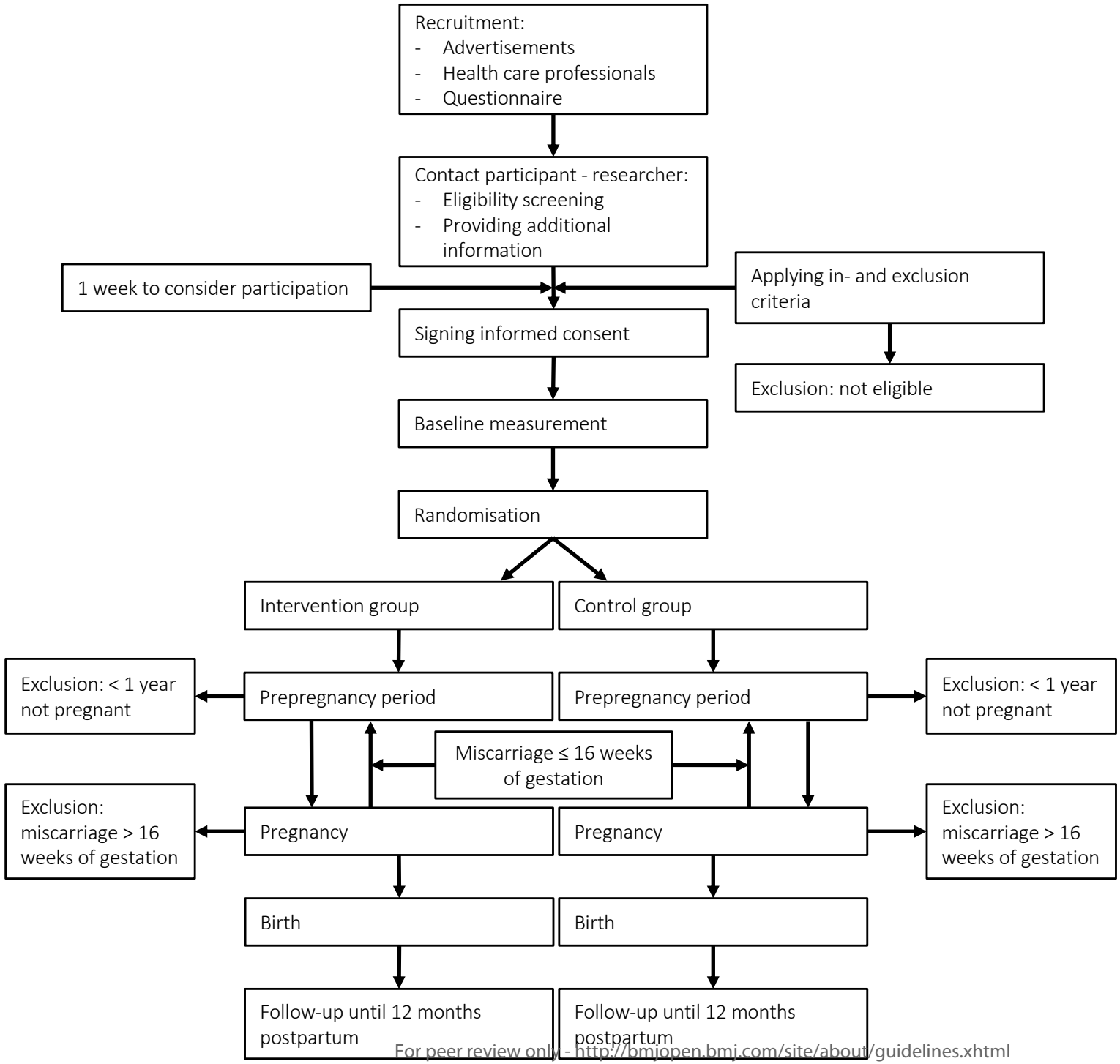
19. Ko TJ, Tsai LY, Chu LC, et al. Parental smoking during pregnancy and its association with low birth weight, small for gestational age, and preterm birth offspring: a birth cohort study. *Pediatr Neonatol* 2014;55(1):20-27. doi: 10.1016/j.pedneo.2013.05.005I
20. Eriksson JG, Sandboge S, Salonen MK, et al. Long-term consequences of maternal overweight in pregnancy on offspring later health: findings from the Helsinki Birth Cohort Study. *Ann Med* 2014;46(6):434-38. doi: 10.3109/07853890.2014.919728I
21. Burdge GC, Slater-Jefferies J, Torrens C, et al. Dietary protein restriction of pregnant rats in the F0 generation induces altered methylation of hepatic gene promoters in the adult male offspring in the F1 and F2 generations. *Br J Nutr* 2007;97(3):435-39. doi: 10.1017/s0007114507352392I
22. Gohir W, Ratcliffe EM, Sloboda DM. Of the bugs that shape us: maternal obesity, the gut microbiome, and long-term disease risk. *Pediatr Res* 2015;77(1-2):196-204. doi: 10.1038/pr.2014.169I
23. Nieuwdorp M, Gilijamse PW, Pai N, et al. Role of the microbiome in energy regulation and metabolism. *Gastroenterol* 2014;146(6):1525-33. doi: 10.1053/j.gastro.2014.02.008I
24. Backhed F, Roswall J, Peng Y, et al. Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. *Cell Host Microbe* 2015;17(5):690-703. doi: 10.1016/j.chom.2015.04.004I
25. i-WIP Collaborative group. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. *BMJ* 2017;358:j3119. doi: 10.1136/bmj.j3119I
26. Getahun D, Ananth CV, Peltier MR, et al. Changes in prepregnancy body mass index between the first and second pregnancies and risk of large-for-gestational-age birth. *Am J Obstet Gynecol* 2007;196(6):530 e1-e8. doi: 10.1016/j.ajog.2006.12.036I
27. Whiteman VE, Aliyu MH, August EM, et al. Changes in prepregnancy body mass index between pregnancies and risk of gestational and type 2 diabetes. *Arch Gynecol Obstet* 2011;284(1):235-40. doi: 10.1007/s00404-011-1917-7I
28. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi: 10.1136/bmj.e7586I
29. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC2013.
30. Statistics Netherlands. StatLine: Birth, key numbers fertility, maternal age, region [Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37201/table?ts=1561462862456 accessed 25-06-2019.
31. Mutsaerts MAQ, van Oers AM, Groen H, et al. Randomized Trial of a Lifestyle Program in Obese Infertile Women. *N Engl J Med* 2016;374(20):1942-53. doi: 10.1056/NEJMoa1505297I
32. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009;374(9702):1677-86. doi: 10.1016/S0140-6736(09)61457-4I
33. Thangaratinam S, Rogozinska E, Jolly K, et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. *BMJ* 2012;344:e2088. doi: 10.1136/bmj.e2088I
34. Vinter CA, Jensen DM, Ovesen P, et al. The LiP (Lifestyle in Pregnancy) study: a randomized controlled trial of lifestyle intervention in 360 obese pregnant women. *Diabetes Care* 2011;34(12):2502-07. doi: 10.2337/dc11-1150I
35. Althuizen E, van der Wijden CL, van Mechelen W, et al. The effect of a counselling intervention on weight changes during and after pregnancy: a randomised trial. *BJOG* 2013;120(1):92-99. doi: 10.1111/1471-0528.12014I
36. Hoeger KM, Kochman L, Wixom N, et al. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. *Fertil Steril* 2004;82(2):421-29. doi: 10.1016/j.fertnstert.2004.02.104I

37. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 2003;348(21):2082-90. doi: 10.1056/NEJMoa022207I
38. Simpson JL. Incidence and timing of pregnancy losses: relevance to evaluating safety of early prenatal diagnosis. *Am J Med Genet* 1990;35(2):165-73. doi: 10.1002/ajmg.1320350205I
39. Zhou H, Liu Y, Liu L, et al. Maternal pre-pregnancy risk factors for miscarriage from a prevention perspective: a cohort study in China. *Eur J Obstet Gynecol Reprod Biol* 2016;206:57-63. doi: 10.1016/j.ejogrb.2016.07.514I
40. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, et al. Subfecundity in overweight and obese couples. *Hum Reprod* 2007;22(6):1634-37. doi: 10.1093/humrep/dem035I
41. Hull MG, North K, Taylor H, et al. Delayed conception and active and passive smoking. The Avon Longitudinal Study of Pregnancy and Childhood Study Team. *Fertil Steril* 2000;74(4):725-33.
42. Nederlandse Vereniging voor Obstetrie en Gynaecologie. Landelijke netwerkrichtlijn Subfertiliteit 2010 [Available from: https://www.nvog.nl/wp-content/uploads/2018/02/Subfertiliteit-landelijke-netwerkrichtlijn-1.0-20-05-2011.pdf.
43. Burke BL, Arkowitz H, Menchola M. The efficacy of motivational interviewing: a meta-analysis of controlled clinical trials. *J Consult Clin Psychol* 2003;71(5):843-61. doi: 10.1037/0022-006x.71.5.843I
44. Miller WR, Rollnick S. Motivational Interviewing, Second Edition: Preparing People for Change: Guilford Publications 2002.
45. Van Dijk MR, Huijgen NA, Willemsen SP, et al. Impact of an mHealth Platform for Pregnancy on Nutrition and Lifestyle of the Reproductive Population: A Survey. *JMIR Mhealth Uhealth* 2016;4(2):e53. doi: 10.2196/mhealth.5197I
46. Van Dijk MR, Koster MP, Rosman AN, et al. Opportunities of mHealth in Preconception Care: Preferences and Experiences of Patients and Health Care Providers and Other Involved Professionals. *JMIR Mhealth Uhealth* 2017;5(8):e123. doi: 10.2196/mhealth.7834I
47. van Dijk MR, Koster MPH, Willemsen SP, et al. Healthy preconception nutrition and lifestyle using personalized mobile health coaching is associated with enhanced pregnancy chance. *Reprod Biomed Online* 2017;35(4):453-60. doi: 10.1016/j.rbmo.2017.06.014I
48. van Dijk MR, Oostingh EC, Koster MP, et al. The use of the mHealth program Smarter Pregnancy in preconception care: rationale, study design and data collection of a randomized controlled trial. *BMC Pregnancy Childbirth* 2017;17(1):46. doi: 10.1186/s12884-017-1228-5I
49. [Available from: www.co-eur.com.
50. The Netherlands Nutrition Centre. De Schijf van Vijf [18-07-2018]. Available from: https://www.voedingscentrum.nl/nl/gezond-eten-met-de-schijf-van-vijf.aspx accessed 18-07-2018.
51. Institute of Medicine. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington (DC): National Academies Press (US) 2009.
52. Shiri R, Coggon D, Falah-Hassani K. Exercise for the prevention of low back and pelvic girdle pain in pregnancy: A meta-analysis of randomized controlled trials. *European Journal of Pain* 2018;22(1):19-27. doi: 10.1002/ejp.1096I
53. Westerterp KR, Wouters L, van Marken Lichtenbelt WD. The Maastricht protocol for the measurement of body composition and energy expenditure with labeled water. *Obes Res* 1995;3 Suppl 1:49-57.
54. Catalano PM, Wong WW, Drago NM, et al. Estimating body composition in late gestation: a new hydration constant for body density and total body water. *Am J Physiol* 1995;268(1 Pt 1):E153-8.
55. van Raaij JM, Peek ME, Vermaat-Miedema SH, et al. New equations for estimating body fat mass in pregnancy from body density or total body water. *Am J Clin Nutr* 1988;48(1):24-9.
56. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* 1982;36(5):936-42. doi: 10.1093/ajcn/36.5.936I

57. Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J Psychosom Res* 1985;29(1):71-83.
58. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. *Lancet* 1998;351(9105):805-06. doi: 10.1016/S0140-6736(05)78933-9I
59. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28(7):412-19.
60. Ben-Shlomo Y, Spears M, Boustred C, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol* 2014;63(7):636-46. doi: 10.1016/j.jacc.2013.09.063I
61. Ding J, Wai KL, McGeechan K, et al. Retinal vascular caliber and the development of hypertension: a meta-analysis of individual participant data. *J Hypertens* 2014;32(2):207-15. doi: 10.1097/HJH.0b013e32836586f4I
62. Nederlandse Vereniging voor Obstetrie en Gynaecologie. Richtlijn Diabetes mellitus en zwangerschap 2018 [Available from: https://www.nvog.nl/wp-content/uploads/2018/10/NVOG-richtlijn-Diabetes-mellitus-en-zwangerschap-v3.0-2018.pdf.
63. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications : report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus 1999 [Available from: https://apps.who.int/iris/handle/10665/66040.
64. Nederlandse Vereniging voor Obstetrie en Gynaecologie. Richtlijn Hypertensieve aandoeningen in de zwangerschap 2011 [Available from: https://richtlijnendatabase.nl/richtlijn/hypertensieve_aandoeningen_in_de_zwangerschap/hypertensieve_aandoeningen_-_startpagina.html.
65. Nederlandse Vereniging voor Obstetrie en Gynaecologie. Richtlijn Foetale groeirestrictie 2018 [Available from: https://www.nvog.nl/wp-content/uploads/2018/08/NVOG-richtlijn-FGR-2017-definitief-incl.-aanpassingen-Doppler-ACM-aug.-2018.pdf.
66. Visser GH, Eilers PH, Elferink-Stinkens PM, et al. New Dutch reference curves for birthweight by gestational age. *Early Hum Dev* 2009;85(12):737-44. doi: 10.1016/j.earlhumdev.2009.09.008I
67. Stocks J, Sly PD, Tepper RS, et al. Infant respiratory function testing. New York: Wiley-Liss 1996.
68. Galley JD, Bailey M, Kamp Dush C, et al. Maternal obesity is associated with alterations in the gut microbiome in toddlers. *PLoS One* 2014;9(11):e113026. doi: 10.1371/journal.pone.0113026I
69. Ley RE. Obesity and the human microbiome. *Curr Opin Gastroenterol* 2010;26(1):5-11. doi: 10.1097/MOG.0b013e328333d751I
70. Lundgren SN, Madan JC, Emond JA, et al. Maternal diet during pregnancy is related with the infant stool microbiome in a delivery mode-dependent manner. *Microbiome* 2018;6(1):109. doi: 10.1186/s40168-018-0490-8I
71. Seganfredo FB, Blume CA, Moehlecke M, et al. Weight-loss interventions and gut microbiota changes in overweight and obese patients: a systematic review. *Obes Rev* 2017;18(8):832-51. doi: 10.1111/obr.12541I
72. Kerr CA, Grice DM, Tran CD, et al. Early life events influence whole-of-life metabolic health via gut microflora and gut permeability. *Crit Rev Microbiol* 2015;41(3):326-40. doi: 10.3109/1040841x.2013.837863I
73. Koren O, Goodrich JK, Cullender TC, et al. Host remodeling of the gut microbiome and metabolic changes during pregnancy. *Cell* 2012;150(3):470-80. doi: 10.1016/j.cell.2012.07.008I
74. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A* 2010;107(26):11971-5. doi: 10.1073/pnas.1002601107I
75. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nat Med* 2016;22(3):250-3. doi: 10.1038/nm.4039I

76. Kon IY, Shilina NM, Gmoshinskaya MV, et al. The Study of Breast Milk IGF-1, Leptin, Ghrelin and Adiponectin Levels as Possible Reasons of High Weight Gain in Breast-Fed Infants. *Annals of Nutrition and Metabolism* 2014;65(4):317-23. doi: 10.1159/000367998I
77. Sadr Dadres G, Whitaker KM, Haapala JL, et al. Relationship of Maternal Weight Status Before, During, and After Pregnancy with Breast Milk Hormone Concentrations. *Obesity (Silver Spring)* 2019;27(4):621-28. doi: 10.1002/oby.22409I
78. Lipkie TE, Morrow AL, Jouni ZE, et al. Longitudinal Survey of Carotenoids in Human Milk from Urban Cohorts in China, Mexico, and the USA. *PLoS One* 2015;10(6):e0127729. doi: 10.1371/journal.pone.0127729I
79. Nelissen EC, Dumoulin JC, Busato F, et al. Altered gene expression in human placentas after IVF/ICSI. *Hum Reprod* 2014;29(12):2821-31. doi: 10.1093/humrep/deu241I
80. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-xI
81. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013;22(7):1717-27. doi: 10.1007/s11136-012-0322-4I
82. Wilkinson MD, Dumontier M, Aalbersberg IJ, et al. The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* 2016;3:160018. doi: 10.1038/sdata.2016.18I
83. Catalano P, deMouzon SH. Maternal obesity and metabolic risk to the offspring: why lifestyle interventions may have not achieved the desired outcomes. *Int J Obes* 2015;39(4):642-49. doi: 10.1038/ijo.2015.15I
84. Temel S, van Voorst SF, Jack BW, et al. Evidence-based preconceptional lifestyle interventions. *Epidemiol Rev* 2014;36:19-30. doi: 10.1093/epirev/mxt003I
85. Hillemeier MM, Downs DS, Feinberg ME, et al. Improving women's preconceptional health: findings from a randomized trial of the Strong Healthy Women intervention in the Central Pennsylvania women's health study. *Womens Health Issues* 2008;18(6 Suppl):S87-96. doi: 10.1016/j.whi.2008.07.008I
86. Lan L, Harrison CL, Misso M, et al. Systematic review and meta-analysis of the impact of preconception lifestyle interventions on fertility, obstetric, fetal, anthropometric and metabolic outcomes in men and women. *Hum Reprod* 2017;32(9):1925-40. doi: 10.1093/humrep/dex241I
87. Mutsaerts MA, Kuchenbecker WK, Mol BW, et al. Dropout is a problem in lifestyle intervention programs for overweight and obese infertile women: a systematic review. *Hum Reprod* 2013;28(4):979-86. doi: 10.1093/humrep/det026I
88. Burgess E, Hassmen P, Pumpa KL. Determinants of adherence to lifestyle intervention in adults with obesity: a systematic review. *Clin Obes* 2017;7(3):123-35. doi: 10.1111/cob.12183I
89. Willeboordse M, van de Kant KDG, Tan FE, et al. A Multifactorial Weight Reduction Programme for Children with Overweight and Asthma: A Randomized Controlled Trial. *PLoS One* 2016;12(7):e0181130. doi: 10.1371/journal.pone.0157158I
90. Hutchinson SG, van Breukelen G, van Schayck CP, et al. Motivational interviewing and urine cotinine feedback to stop passive smoke exposure in children predisposed to asthma: a randomised controlled trial. *Sci Rep* 2017;7(1):15473. doi: 10.1038/s41598-017-15158-2I
91. Rijks JM, Plat J, Mensink RP, et al. Children With Morbid Obesity Benefit Equally as Children With Overweight and Obesity From an Ongoing Care Program. *J Clin Endocrinol Metab* 2015;100(9):3572-80. doi: 10.1210/jc.2015-1444I





Supplement 1: SPIRIT checklist

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 3
	2b	All items from the World Health Organization Trial Registration Data Set	Page 3
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	Page 20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, page 20
	5b	Name and contact information for the trial sponsor	Page 20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 5 & 6
	6b	Explanation for choice of comparators	Page 7
Objectives	7	Specific objectives or hypotheses	Page 7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 7 & 8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 9-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 18 & 19
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 12-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Not applicable
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Not applicable
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 18 & 19

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Not applicable
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 7
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not applicable

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	-
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page 16

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Supplement 2: Informed consent form "TOP-mums, for a healthy start"

Child

I have been asked to consent to the following person/my child participating in this medical-scientific study.

Name of study subject (child): Date of birth: ____ / ____ / _____

- I have read the subject information form for the parents/guardians. I was able to ask questions. My questions have been answered to my satisfaction. I had enough time to decide whether I want my child to participate.
- I know that participation voluntary. I know that I may decide at any time that I do not want my child to participate after all or to withdraw from the study. I do not need to give a reason for this.
- I give permission for my child's general practitioner/treating specialist/youth health care division to be informed about my child's participation in this study.
- I know that some people may have access to all data of my child to verify the study. These people are listed in the information letter and the Brochure "Medical Research: General information for subjects". I consent to the inspection by them.
- I approve that my child's data will be used in order to achieve the goals as described in the information letter.
- I give permission for information to be requested from my child's youth health care division as described in the information letter.
- I approve that my child's data that will be collected during this study, will be stored for 15 years.
- I **do/do not*** consent to keeping my child's bodily material that will be collected during the study for 15 years after the end of this study. In the future, the bodily material may be used for research questions in line with this study.
- I **do/do not*** approve to be approached for further research.

* Please cross the option that is not applicable.

I agree to this person's/my child's participation in this study.

Name of the parent/legal guardian:

Signature: Date: ____ / ____ / _____

Name of the parent/legal guardian:

Signature: Date: ____ / ____ / _____

I declare that I have fully informed the abovementioned persons about the study referred to.

If information becomes available during the study that could affect the parent's or guardian's consent, I will notify him/her about this in good time.

Name of investigator (or his/her representative):

Signature: Date: ____ / ____ / _____

If applicable, additional information was given by:

Name:

Job title:

Signature: Date: ____ / ____ / _____

Supplement 3: Informed consent form "TOP-mums, for a healthy start"

Women who plan to conceive

- I have read the subject information form. I was able to ask questions. My questions have been answered to my satisfaction. I had enough time to decide whether to participate.
- I know that participation is voluntary. I know that I may decide at any time not to participate after all or to withdraw from the study. I do not need to give a reason for this. When I decide to quit my participation, this will not have any influence on the usual care for me.
- I know that, when I decide to quit my participation, the researcher may ask me to complete questionnaires regarding expenditures in terms of my pregnancy and child.
- I give permission for my general practitioner, midwife and treating specialist to be informed that I am participating in this study.
- I agree that my general practitioner and/or treating specialist will be informed of coincidental findings that may be of interest for my health.
- I know that some people have access to all my data to verify the study. These people are listed in the information letter and the Brochure "Medical Research: General information for subjects". I consent to the inspection by them.
- I approve that my data will be used in order to achieve the goals as described in the information letter.
- In addition, I approve that my personal and medical information, as described in the information letter, will be retrieved from my midwife and/or my gynaecologist.
- I know that the researcher will approach me after my delivery, to ask for informed consent for participation of my child in the study.
- I approve that my data that will be collected during this study, will be stored for 15 years.
- I **do/do not*** approve to store my human tissue that will be collected during the study for 15 years after the end of this study. In the future, the human tissue may be used for research questions in line with this study.
- I **do/do not*** desire to be informed about the results of the study.
- I **do/do not*** approve to be approached for further research.

* Please cross the option that is not applicable.

I want to participate in this study.

Name of study subject:

Signature: Date: ____ / ____ / _____

I hereby declare that I have fully informed this study subject about this study.

If information comes to light during the course of the study, that could affect the study subject's consent, I will inform her of this in a timely fashion.

Name of investigator (or his/her representative):

Signature: Date: ____ / ____ / _____

If applicable, additional information was given by:

Name:

Job title:

Signature: Date: ____ / ____ / _____

Supplement 4: Consultations with personal lifestyle coach and dietician

	Preconception							During pregnancy								Postpartum						
	Baseline	1 month	2 months	3 months	6 months	9 months	12 months	6 weeks	12 weeks	16 weeks	20 weeks	28 weeks	32 weeks	36 weeks	38 weeks	1 month	3 months	4 months	6 months	7.5 months	9 months	12 months
Personal lifestyle coach	x	x	x	x	x	x	x	x	x	x	x		x	x		x	x		x		x	x
Dietician	x	x		x	x	x		x	x		x	x		x		x		x		x		

Supplement 5: Questions screening eating disorder

1. Are you unsatisfied about your eating habits?
2. Do you ever eat secretly?
3. Does your body weight have influence on your emotional feelings?
4. Do you think that eating plays an important role in your life?
5. Have you ever been afraid of losing control of your eating behavior?
6. Have you ever had binge eating?
7. Do you ever have feelings of shame or guilt when you have eaten?
8. Have you ever had trouble concentrating because you had to think about food?