UNIVERSITY OF COPENHAGEN
DEPARTMENT OF NUTRITION, EXERCISE AND SPORTS

Participant Information

For the mother's, (father's,) and child's participation in PREPARE CHILD – CPH

The effect of weight loss before pregnancy on childhood health

Read this information material thoroughly before deciding whether you want to participate.

Original title: PRE-Pregnancy weight loss And the Reducing Effect on CHILDhood overweight – a randomized controlled study in Copenhagen

Department of Nutrition, Exercise and Sports (NEXS)
Faculty of Science
University of Copenhagen

Department of Gynaecology-Obstetrics
Hvidovre Hospital

PREPARE CHILD – PIXI-edition

The aim of the project

In PREPARE CHILD - CPH we will investigate how weight loss prior to conception will affect health for you as the prospective mother (and perhaps father), the journey to becoming pregnant, the pregnancy itself and the planned child's health.

What does the project imply?

We will follow 240 women/couples and their planned child from the time they plan pregnancy and until the child is 18 months old.

Which examinations will there be in the project?

Every participant will during pregnancy receive health examinations of both the mother/father and your planned child. The table generally illustrates which measurements take place in the various phases of the study.

Lots will be drawn so that 120 females/couples will enter the intervention group and 120 females/couples will enter the control group.

The intervention group is expected to lose approximately 10% using a formula diet the first three months before trying to become pregnant. Here after the weight loss must be maintained with the help of dietitian guidance and a diet rich in protein and dietary fibres.

The Control group must live as they normally do and can try to become pregnant after the first examination day.

What do you get out of participating in the project?

All participants will receive thorough examinations of the health of the woman, perhaps the man, and the planned child during and after pregnancy.

Is there any risk in participating in the project?

There is no known serious risk of participating in the project. When taking a blood sample, there may be mild pain and a very small risk of infection. The project has been approved by the Scientific Ethics Committee and follows current ethical guidelines. Information regarding study participants is protected according to the General Data Protection Regulation/ GDPR www.retsinformation.dk.

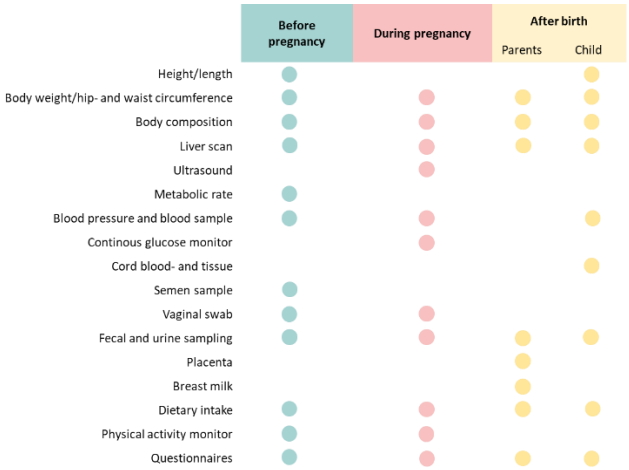


TABLE OF CONTENT

PREPARE CHILD – PIXI-EDITION 2

PREPARE CHILD - CPH 3

THE EFFECT OF WEIGHT LOSS BEFORE PREGNANCY ON THE CHILD'S HEALTH 3

AIM OF THE TRIAL 3

AS A PARTICIPANT, WHAT DO YOU GAIN? 4

HOW IS THE PROJECT CARRIED OUT? 4

DURATION OF THE TRIAL 5

WHO CAN PARTICIPATE? 6

WHAT DOES THE PROJECT ENTAIL FOR YOU AND YOUR PLANNED CHILD? 7

COURSE OF THE STUDY AND ACTIVITIES 8

MEASUREMENTS AND RISKS 15

DATA HANDLING 15

RESEARCH BIOBANK 16

INSURANCE AND AVENUES OF COMPLAINT 17

ECONOMIC CIRCUMSTANCES 17

PUBLICATIONS OF RESULTS 17

IF YOU WANT TO KNOW MORE 18

PREPARE CHILD - CPH

The effect of weight loss before pregnancy on the child's health

You have received this participant information as ***you plan on becoming pregnant within the next year*** *and have shown your interest for the project PREPARE CHILD – CPH Weight loss before pregnancy to reduce childhood obesity. We therefore invite you to participate in PREPARE CHILD – CPH.*

Before deciding upon whether you would like to participate, we kindly ask you to read through this information guide and the "Subjects rights in a health scientific research trial", that is provided by the Danish National Centre for Ethics committee system.

Participation requires that you and your planned child take part in various examinations until the child is 18 months. For the child to participate, those who hold parental authority (from here parents) should give permission that the child can participate. Thus, we ask you to read through this participant information thoroughly.

It is voluntary to participate and at any given point you can withdraw your own and your child from the project without consequence.

Aim of the trial

In PREPARE CHILD - CPH we will investigate how weight loss prior to conception will affect health for you as the prospective parent(s), the journey to becoming pregnant, the pregnancy itself and the planned child's health.

The multicentre study PREPARE CHILD - Denmark consists of the PREPARE CHILD - CPH research project conducted in collaboration with PREPARE CHILD – AUH. The multicentre project is a collaboration between the University of Copenhagen, The Capital Region of Denmark (Hvidovre Hospital and Rigshospitalet), The

Aarhus University, Steno Diabetes Center Aarhus, and Central Denmark Region.

Background of the project

Women with overweight have a higher risk of complications throughout pregnancy and during birth compared to women with normal weight. Further, women with overweight tend to gain excess weight during pregnancy and give birth to larger babies. These two factors are suggested to contribute to increased risk of overweight and e.g. diabetes for the children later in life. Recent research has shown that the paternal weight and health plays a role in the growth and development of the foetus and later health of the child. It is suggested that it might be the 'programming' of the child.

Studies of people with overweight have shown that weight loss benefits the body's metabolism, which can positively impact the sperm and the environment of which the egg grows in. It is important that the diet which the woman consumes during pregnancy, contribute everything necessary to both mother and child. We know, that by following the recommended guidelines, the pregnant woman and the foetus will get all the necessary nutrients and the weight gain will be limited. New research suggests that diets with extra protein and many fibres can help regulate appetite and therefore prevents excess weight gain during pregnancy.

Approximately half of all adults are overweight, and so it comes with good reason to investigate whether weight loss in the prospective parents *prior* to conception can contribute to the reduction in obesity and co-morbidities in the child.

As a participant, what do you gain?

The project will provide significant knowledge and understanding regarding the importance of weight loss for the woman's and the man's ability to conceive, the pregnancy itself and the planned child's health. A better understanding of this will provide new knowledge regarding the possibility of prevention of overweight in the coming generations, the interplay between the parents' metabolism and the ability to conceive. All women will receive dietary guidance during pregnancy and will receive the vitamins and minerals that are recommended to be taken whilst planning to conceive and whilst pregnant, and a guidance to breastfeeding prior to birth. The male will also receive vitamin D. As participant(s), you will receive thorough health checks of the planned child's growth and development from conception and until it is 18 months old. Early in this period, you will also receive dietary guidance in transitional diet to the child. No financial compensation will be given for the participation. However, upon completion of the study, when the child is 18 months, a present will be provided, worth no more than 200 D.kr.

How is the project carried out?

In the research project, PREPARE CHILD – CPH we will follow 240 females/couples and their planned child through a period of approximately 3 years; from the planned pregnancy and until the child is 18 months old.

Those interested in the trial should attend an information meeting at the Department of Nutrition, Exercise and Sports (NEXS), Frederiksberg. Those females/couples who wish to participate and match the criteria (decided at a screening visit), will be divided into two groups. In one group, the intervention group, the female (and perhaps the male) is expected to lose approximately 10% of their body weight, with the help of a formula diet for the first three months,

prior to conception. If the male participates in the trial and has a BMI< 25 kg/m^{2,} he will be guided in weight maintenance and will not follow the formula diet. Following this, weight loss should be maintained with help from dietician guidance and a diet high in protein and fibre. The other group, the control group will be asked to live as usual until registration of pregnancy. When pregnancy is registered the control group will follow the same program as the intervention group throughout the trial. The control group is allowed to try to conceive following the first examination day. You are not able to choose group yourself – this is decided by lot.

Participation in the intervention group will require visits every 2nd week, with dietary guidance, various measurements, and questionnaires throughout the first three months. In the following months (up until month 12), until conception, and whilst pregnant, visits will take place once a month. Each visit can take 1-2 hours. For all participants, there will be thorough examinations at the beginning, after 3 months (only intervention group), and two times throughout pregnancy. Each of these examinations may take up to 3 hours. At birth, and when the child is 3, 6, 12 and 18 months old, you and your child will visit us again, so that we can take various measurements from the child and complete examinations of you. Each of these visits can take up to 2.5 hours.

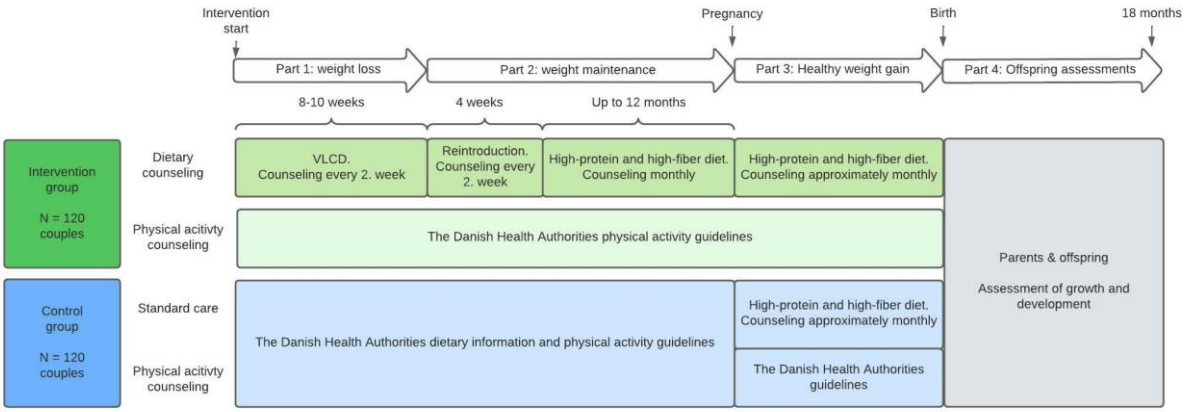
Most of the examinations will take place at the Department of Nutrition, Exercise and Sports (NEXS), Frederiksberg. In addition to the birth, all females will have up to 5 examinations at Hvidovre Hospital. Males have, in addition to the birth, up to four examinations and Hvidovre Hospital and up to three examinations will take place at Rigshospitalet. Examinations of the child will mainly be at the Department at Frederiksberg and in addition to the birth there will be up to three examinations at Hvidovre hospital.

Information meetings, dietary guidance, examinations, and the activities that take place are explained below.

Duration of the trial

The project was initiated in September 2022, but recruitment is running continuously. The last participant is planned to finish in the end of 2027. The research period for each participant will last approximately 3 years and will consist of 33 visits for the intervention group and 16 visits for the control group. Participation in the trial is possible if you plan to conceive within the next year and match the criteria. If you become pregnant within 12 months, your participation in the project will continue throughout the approximate 9 months of pregnancy and finally, you and the child will be examined until the child is 18 months old. If we later obtain more funding, we will conduct a follow-up trial where your child will be examined later in childhood. We will therefore ask for your

Figure 1: Overview of the PREPARE CHILD process



permission to contact you if it becomes relevant. However, it is of course voluntary, and it has no influence on whether you and your child can participate in this trial.

Who can participate?

Female

As a prospective mother you can participate in the project if you

- Are between 18-38 years old
- Have a BMI between 27.0 - 44.9 kg/m^2
- Are planning to get pregnant within 1 year
- Are affiliated with Hvidovre Hospital or are willing to seek permission to give birth at Hvidovre Hospital
- Do not have diabetes
- Are in good health
- Are prepared to allow your planned child to participate in the project

Male

As a prospective father you can participate in the entire project (full participation) if you

- Are between 18-55 old
- Have a BMI between 18.5 - 44.9 kg/m^2
- Are planning pregnancy within 1 year
- Do not have diabetes
- Are in good health
- Are prepared to allow your planned child to participate in the project

Or you can participate partly, where you provide information about yourself via a questionnaire, but do not participate in examinations and consultations which are related to males.

There are no criteria related to age, BMI etc. if you participate partly.

Child

Your planned child will automatically participate in the project by participating in child examinations from birth to the child is 18 months of age.

To participate it is further required

- That you speak and understand either Danish or English. All written and oral information including questionnaires will be provided in either language.
- That you are willing to store your child's urine and faeces samples in a small, sealable container, in your own freezer until the following visit, which could be up to 2 months after collection of the sample.

It's *not* possible to participate if you match any of the following:

- Currently pregnant or breastfeeding
- Do not wish to allow the planned child to partake in the project
- Participate in elite sports or similar strenuous exercise ≥ 5 hours per week
- Have experienced fluctuating weight of over 5% of your body weight within the last 3 months
- Are on a diet, have allergies or intolerances, that mean you cannot follow the studies instructions
- Have a milk or soya allergy
- Have diabetes
- Are diagnosed with a thyroid, heart, liver, or kidney disease
- Are or have been diagnosed with an eating disorder.
- Are an active blood donor throughout the project
- Simultaneously participating in other clinical projects
- Receiving IVF (test tube processing)
- Have had ≥4 spontaneous miscarriages (coherent/in a row)

Further exclusion criteria may be assessed at the screening visit after participation in an information meeting.

As a male, it is not a requirement to participate in the project, which means that a woman can participate alone with the future child as long as

both holders of parental custody provide consent to this. However, we would like to encourage the male (the father-to-be) to participate, as it will in many ways strengthen and support the woman. For fathers-to-be who do not wish to participate in the entire project (e.g. because they do not meet the above criteria or cannot allocate the time), we will greatly appreciate that they participate partially where they via a questionnaire share relevant health information that may be of importance for examination of the future child health.

Exclusion from the project

If the female and the future child do not fulfil the stated criteria for participation in the trial, then neither the female, the male nor the child can participate.

As a participant you will be excluded from further participation if pregnancy is confirmed 4 weeks after the baseline visit and/or you become pregnant with more than one child. In case conception does not happen within 12 months after the baseline visit (control group) or following weight loss (intervention group), if you do not follow the guidelines for the intervention, become ill or if any unforeseen circumstances occur, which result in you not being able to complete the project, you will also be excluded. You may also be discontinued from participating in the project if you do not follow the project guidelines. In the event of exclusion from the trial, you will be informed of the reason.

What does the project entail for you and your planned child?

In the following sections, the activities which require your participation throughout the trial will be described. The activities will be explained in details and follow a chronological order.

Information meeting

To participate in the trial, you should plan to conceive within the next year. You are required to participate in an obligatory information meeting, *before* you as a woman become pregnant. At the information meeting you will receive information regarding the trial, the purpose, course, examinations, and activities of the trial. The information meeting will last approximately 2 hours. The meeting will be held by qualified project personnel and will take place individually or in smaller groups. There will be an opportunity to ask questions, also in private. In case the prospective father does not want to participate in the project, we still encourage him to participate in the information meeting and you are also welcome to bring a friend or family member along.

Informed Consent

If you, after the information meeting, decide to participate in the upcoming trial, you will be required to sign an informed consent. You have the right to take consideration time before you decide. If you do not wish consideration time, then you are welcome to sign the informed consent following the information meeting. Only then, your eligibility to all inclusion and exclusion criteria will be evaluated. Before your planned child can participate in the project, it is essential that all holders of parental authority sign the informed consent. This is only necessary once expecting your planned child. It is also possible to sign a power of attorney so that one authority holder can sign for both parties.

Random assignment

The group you are assigned to will be randomly determined; 50% of participants will be assigned to the intervention group and 50% to the control group. Couples will be placed in the same group. Only those in the intervention group will receive dietary guidance before pregnancy; however, everyone will receive dietary guidance throughout pregnancy. Further, everyone will receive the same examinations of the female's, the male's, and the expected child's health throughout pregnancy.

Method for weight loss in the intervention group

Those participants who are required to lose body weight in the first part of the study will follow a formula diet (NUPO). This method ensures a rapid weight loss with the help of diet supplemental products consisting of very few calories (very low-calorie diet, VLCD). The aim of this is to allow you as the prospective mother a substantial weight loss of approximately 10% over a period of 8 weeks. If you as the prospective father has a BMI above 25 kg/m^2 then you will also follow a VLCD alongside the prospective mother, until your BMI ≤23 kg/m^2 or you have obtained a weight loss of approximately 10% of your body weight. NUPO can come in the form of soups or shakes and with different tastes. The diet will consist of 6 small NUPO-meals a day, which replaces all your food for that period. You will have a choice of flavours. It is recommended to drink approximately 1.5-2 litres of water, coffee, tea, or no-calorie drinks throughout the diet. It is important that you can consume milk and soya, due to the formula diet including them or having traces. During the weight loss period you are not allowed to become pregnant. Pregnancy tests will be used before the weight loss is initiated and after 4 weeks. Furthermore, pregnancy tests may be performed continuously if the female participant or the project staff in this period judge that there is a reasonable possibility of pregnancy. This is done for the safety of the possible foetus.

Diet for maintenance of weight loss

Following the weight loss, comes 4 weeks of reintroducing food into the diet. After this you will receive dietary advice once a month where it will be recommended you follow a diet high in protein and fibre. This diet will help you to maintain the weight lost.

Diet for the control group

Participants allocated to the control group will not follow the formula diet and will not receive any form of dietary advice prior to conception. You will be asked to continue as usual, until pregnancy is registered. After this you will follow the same dietary program during pregnancy as participants in the intervention group; and you will receive the same recommended vitamins and minerals. In the period prior to pregnancy, you will be invited to physical visits at NEXS to receive your nutritional supplements and at the same time have your body weight measured. These meetings are planned every 3rd month and there will be two of these meetings (see below).

Vitamin and mineral supplements

All participating females will receive supplements, which are recommended on a daily basis: folic acid from project start to the beginning of the second trimester, iron and vitamin D from project start and throughout pregnancy. Participating males will receive vitamin D tablets from project start until registration of pregnancy.

Course of the study and activities

Participation in the study will last up to 12-15 months prior to the planned pregnancy and until your child is 18 months old; in total this will be approximately 3 years. Couples will be assigned to the same group, either the intervention or the control group and they will stay in this group throughout the study. When you participate in the study you will attend meetings with a dietician before (only the intervention group) and during pregnancy, whilst also participating in the planned measurements and examinations.

Figure 1 is an overview of the course of the project and in the schedules on the following pages you can see which specific examinations that are planned for both the female, the male and your planned child.

Examination days at NEXS

Prior to the large examination days, all fully participating parents will be asked to complete the questionnaires and collect a stool sample. The stool sample will be handed over at the start of the examination to project personnel at NEXS. Afterwards, the questionnaire will be discussed to ensure all is clear and no questions remain. You will then be measured and weighed. Your blood pressure and heart rate will be measured, and a blood sample will be drawn. You will be asked to provide a urine sample, and females will be asked for a vaginal swab and breast milk. In relation to the large examination days, males will be asked to go to Rigshospitalet and provide a semen sample. On the first trial day, following weight loss (only the intervention group), and following the birth, a scan that shows your body composition will be conducted. At the first trial day and for the intervention group also after weight loss, you will have your resting metabolism measured.

When pregnancy is registered

When your register pregnancy, we ask you to contact us by sending an SMS to us on the phone number **+45 51 48 93 80.** The message should include your participant number. Project personnel will contact you to schedule future examination days.

When the birth begins

If you become pregnant and reach to the start of delivery, it is important that you send an SMS to us on the phone number **+45 51 48 93 80**. The message must include information regarding your participant number, which hospital you will be going to and when you expect to arrive. Following the birth of your child, you will be contacted by the project personnel who will measure length, weight and body composition of the child. In addition to this, measure and weigh fully participating parents; these measurements will take place at the hospital before you go home.

Measurements and examinations

Weight, height/length, circumference, and skinfolds measurements.

Your height will be measured at the screening visit (visit -1) and at baseline (visit 0). Hip-waist measurements will be registered at baseline, at several visits both before, during and after pregnancy. The weight will be registered at screening, baseline and at each visit after the project starts; and your child will be measured a total of five times. The control group will be asked to register their body weight at home in the period prior to registered pregnancy. Waist circumference will not be measured on the prospected mother during pregnancy. The child's skinfolds on the arm, shoulder blade, hip and stomach will be measured with the help of a handheld equipment. We will measure the child's length, lower leg length, circumference of head, thigh, upper arm, waist, and hip with a measuring tape. The measurements taken are simple, which are carried out using suitable measuring equipment and is not expected to cause discomfort. The aim of these measurements is to follow the development of the child's body composition and growth.

Dietary registry

Your(s) and the child's dietary intake is registered in connection with the other examinations via an electronic questionnaire or a 24-hr dietary recall interview conducted by trained personnel before, during and after pregnancy. There will also be a questionnaire regarding the child's dietary intake at the child's visits at 6, 12 and 18 months.

Physical activity

You will answer a questionnaire about physical activity up to eight times throughout the project. In addition, you will have your physical activity and sleep measured at least four times with the help of an activity monitor which should be worn for 7 days and 8 nights. The activity monitor should only be removed when showering. The

aim is to determine how much and at which intensity you are moving and what your sleep pattern look like. Despite annoyance with wearing this for several days, there are no expected inconvenience with this examination.

Resting metabolism
Resting metabolism will be measured with the help of indirect calorimetry, which measures the in- and exhaled air. With this measurement the bodies energy metabolism at rest will be measured, and we will measure the intervention group before and after weight loss. The control group's resting metabolism will only be measured at the project start.

Scans
Body composition will be measured on both you and the child with the help of a DXA-scanner. In addition, an ultrasound will be performed of the foetus. At these examinations, the parental and foetus body composition like fat mass, muscle mass, bone health will be measured, and in addition the growth and development of the foetus will be measured.

Ultrasound
Ultrasounds will be performed at Hvidovre Hospital by trained professionals. An ultrasound is requested at 28 weeks, to determine the growth of the foetus. During the ultrasound you will be asked to lie on your back where the skin of the stomach will be scanned. The scan will send sound waves through the body, which cannot be heard by the human ear. The sound waves will create an echo which is translated into a live black and white photo on a computer screen. There are no known risks connected to the ultrasound scan for neither mother nor foetus (ACOG Committee on Obstetric Practice 2004). Neither with repeated measurements taken throughout the pregnancy. Based on previously experience, the majority of pregnant women who have been scanned tend to be extremely happy to have the opportunity to see images of their foetus.

Ultrasound of the liver
Ultrasound scanning of the liver will be performed both before, during, and after pregnancy at Hvidovre Hospital and will be performed by trained staff. Adult participants will be scanned up to 4 times and children will be scanned a total of 2 times during the study period. The measurement takes place by placing the person on a bed on the back, after which the liver (the right part of the upper abdomen) is scanned on the abdominal skin. The scanner sends sound waves into the body, thereby measuring the composition of the liver. There is no discomfort associated with the ultrasound scan and it is safe for both pregnant women and children to be scanned.

DXA scan
All DXA scans will be conducted at NEXS, Frederiksberg by trained professionals. In total, male participants in the intervention group will be DXA scanned four times during the trial; two prior to conception, one during pregnancy and one shortly after the birth and females in the intervention group will be DXA scanned three times in total; two times prior to conception and one shortly after birth. The female and male in the control group will be scanned two times (before pregnancy and shortly after birth) and three times (before pregnancy, during pregnancy and after birth), respectively. When the child is 6, 12 and 18 months old, it will be DXA scanned (should a scan fail, one re-scan per examination will be performed).

A DXA scan measures body composition (fat-, muscle- and bone mass) by X-ray radiation.

Figure 2: DXA scanner

During a DXA-scan, you will be exposed to a maximum radiation of 0.006mSv and 0.0004mSv for adults and child, respectively, which constitutes a very modest amount of radiation. According to the international commission for the radiation protection guidelines, the risk of terminal radiation induced cancer is increased by 5% at an effective dose of 1000mSv in a normal population, which would suggest that the risk for these DXA scanned patients is extremely small.
In comparison, a standard X-ray of the heart and lungs, gives an X-ray radiation frequency of 0.300mSv. The daily background radiation in Denmark is 0.008mSv which would imply that radiation from the DXA-scan in this trial is equivalent to 18 hours and 1.25 hours of background radiation for adults and children, respectively. The female will be asked to take a pregnancy test before the scanning is processed; and only with a negative test the scan will be conducted. The scan will be conducted by trained professionals and will last approximately 15 minutes. If the first scan is not successful, then only one re-attempt will be made.

Pod measurement
The body composition of the child will be measured using a PeaPod/BodPod, which uses air displacement technology to determine the child's fat and fat-free mass. The child and parents can have eye contact throughout the measurement, which take approximately 2 minutes in the preheated cabin. There are no risks with these measurements, no radiation, pressure, or noise. If the measure fails at an examination, will the measure be repeated once per examination.

Figure 3: Measurement of body composition of the child during Pod measurements

Faeces and urine sample
All participants should collect and deliver faeces and urine samples throughout their participation in the project; the female four times (three for those in the control group), the male three times (two for those in the control group) and from the child faeces and urine samples will be collected six times. In the faeces sample we will investigate the intestinal microbiota (e.g. the number and composition of intestinal bacteria) and the breakdown of products from the body (metabolites). In the urine samples we will investigate for metabolites.

Breast milk
Breast milk is collected by pumping milk from one full breast using an electric breast pump. After pumping out, 30 ml will be saved for analysis, the rest will be offered to the child. The breast milk samples are collected at the first three examination visits after birth (6 days after birth, as well as 3 and 6 months after birth). In the breast milk components that can estimate whether breastfeeding is established, as well the composition of other bioactive components that may be of importance to the child's growth, e.g. hormones are measured.

Table 1: Overview of visits, examinations, and measurements for the intervention group

Visit number	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27		28	29	30	31
		Weight loss									Weight loss maintenance - before pregnancy											Pregnancy								After birth					
Week in project			1	2	4	6	8	10	12	14																								
Week in trial, following weight loss											4	8	12	16	20	24	30	36	42	48	52													
Pregnancy, weeks																							8	13	20	28	36	39						
Child's age, months																													0	1	3	6	12	18
Background		F/M																																
Height/length*	F/M	F/M																											C		C	C	C	C
weight*	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M/C		F/M/C	F/M/C	F/M/C	F/M/C
Hip and waist measurements		F/M					F/M	F/M	F/M	F/M				F/M				F/M				F/M		F/M			F/M		F/M/C		F/M/C	F/M/C	F/M/C	F/M/C
Dietician councelling		F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M						
Medication use	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M/C		F/M/C	F/M/C	F/M/C	F/M/C
Registry of pregnancy																						F												
Body composition		F/M								F/M												M							F/M/C		C	C	C	C
Ultrasound																										F								
Lever scan		F/M								F/M											F/M				F/M						F/M/C			C
Weight, circumferences- and skinfolds																													C		C	C	C	C
Resting metabolism		F/M								F/M																								
Blood pressure and blood sample		F/M								F/M																	F/M					C	C	C
Continously blood sugar measurement																										F								
Umbilical cord blood and tissue																													C					
Semen sample		M								M			M																					
Vaginal swab (self-taken)		F								F														F			F							
Faeces- og urine sample		F/M								F/M																	F		C	C	C	C	F/M/C	C
Placenta																													F					
Dietary intake/interview		F/M								F/M														F/M			F/M		C		C	C	F/M/C	F/M/C
Physical activity and sleep (aktivity meter)		F/M								F/M														F			F							
Questionnaires		F/M								F/M														F/M			F/M				F/M/C	F/M/C	F/M/C	F/M/C
Breast milk																													F		F	F		
Development, sleep and examinations																																C	C	C

F: Female; M: Male; C: Child. Males with partial participation have no visits and examinations but complete a questionnaire when their female partner has visit 0 and 20.

*After the follow-up visit when the child is 18 months old and until they are 14 years old, we will conduct an annual telephone follow-up call to collect the child's height and weight (self-reported)

Table 2: Overview of visits, examinations, and measurements for the control group

Visit number	-1	0	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27		28	29	30	31
		Before pregnancy												Pregnancy							After Birth					
Week in project			4	8	12	16	20	24	30	36	42	48	52													
Pregnancy, weeks															8	13	20	28	36	39						
Child's age, months																					0	1	3	6	12	18
Background		F/M																								
Height/length*	F/M	F/M																			C		C	C	C	C
weight*	F/M	F/M			F/M				F/M					F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M/C		F/M/C	F/M/C	F/M/C	F/M/C
Hip and waist measurements		F/M												F/M		F/M			F/M		F/M/C		F/M/C	F/M/C	F/M/C	F/M/C
Weigth (self-reported)*			F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M													
Dietician councelling														F/M	F/M	F/M	F/M	F/M	F/M	F/M						
Medication use	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M	F/M/C		F/M/C	F/M/C	F/M/C	F/M/C
Registry of pregnancy														F												
Body composition		F/M												M							F/M/C		C	C	C	C
Ultrasound																		F								
Lever scan		F/M											F/M				F/M						F/M/C			C
Weight, circumferences- and skinfolds																					C		C	C	C	C
Resting metabolism		F/M																								
Blood pressure and blood sample		F/M																	F/M					C	C	C
Continously blood sugar measurement																		F								
Umbilical cord blood and tissue																					C					
Semen sample		M			M																					
Vaginal swab (self-taken)		F														F			F							
Faeces- og urine sample		F/M																	F		C	C	C	C	F/M/C	C
Placenta																					F					
Dietary intake/interview		F/M														F/M			F/M		C		C	C	F/M/C	F/M/C
Physical activity and sleep (aktivity meter)		F/M														F			F							
Questionnaires		F/M														F/M			F/M				F/M/C	F/M/C	F/M/C	F/M/C
Breast milk																					F		F	F		
Development, sleep and examinations																								C	C	C

F: Female; M: Male; C: Child. Males with partial participation have no visits and examinations but complete a questionnaire when their female partner has visit 0 and 20.

*After the follow-up visit when the child is 18 months old and until they are 14 years old, we will conduct an annual telephone follow-up call to collect the child's height and weight (self-reported)

The child's development

All participating parents will record their child's gross motor development and introduction to specific foods using a simple questionnaire, complete a language assessment questionnaire at 6, 12 and 18 months and record five days of sleep patterns in the run up to each assessment visit at 6, 12 and 18 months. At NEXS, the 6-, 12- and 18-month-olds will play a game with a blanket and toys, during which they will be filmed for subsequent assessment of the child's development.

Blood samples

Blood samples will be taken by trained bio analysts. Each adult participant will have a maximum blood volume of 75 mL drawn throughout the project (maximum 25 mL at each sampling session). In the case of the child, the first blood sample will be taken at the time of birth, when blood will be drawn from the umbilical cord after it has been severed from the child. At 6, 12 and 18 months of age, a small sample of blood is taken from the child. At 6, 12 and 18 months, a small sample of blood is taken from the arm after the child has had local anaesthetic patches or cream (EMLA) applied. Children under the age of one year will also be offered water with sugar as analgesic for the blood sampling. The blood is tested for various markers of nutritional status, growth, and health. In preparation for blood sampling, you must arrive at the institute fasted and having done minimum physical activity. Being fasted means not consuming food or drink (other than ½ L of water) after 10pm the night before.

In addition, 48 hours before the visit, you must refrain from strenuous physical activity and alcohol consumption. The baby should not fast before the blood test, but at the 6-, 12-, and 18-month visit, the child should not have had any food or drink other than water for two hours before the examination.

Continuous blood glucose measurement

During pregnancy, the female will have her blood glucose measured once using a continuous glucose monitor. The monitor is attached to the upper body by the project staff and worn for a maximum of 14 days, after which the monitor is removed and returned for the next examination visit. The monitor will measure blood glucose using a small sensor placed just under the skin.

Cord tissue

Just after birth we will take a sample from the umbilical cord tissue.

Placenta samples

Just after birth, the placenta will be weighed, and we will take samples from it.

Vaginal swab

The female in the intervention group and the control group will be instructed to perform four and three vaginal swabs, respectively, during the project. The vaginal swabs will be examined for the composition of microorganisms.

Sperm sample

The male in the intervention group must come to Rigshospitalet three times and deliver a sperm sample, while the male in the control group must deliver two sperm samples. The quality of the semen sample is best if you have not had ejaculation 48 hours before the sample is taken. If the semen sample is not taken at Rigshospitalet, it must not be more than 1 hour old and must be kept at body temperature from the time it is taken until it is given.

Information from medical journals

We will during the project have access to your medical journals with the purpose of gather information of relevance to the study. It can e.g. be information about results of examinations, the

child's growth, blood samples, possible complications, and type of delivery.

Questionnaires
During your participation, you will answer questionnaires about your household, diet, physical activity, sleep, stress, illness, etc., and about your child's diet, physical activity, sleep, illness/medication use, well-being, and development. The completed questionnaires will be reviewed upon receipt by project staff for any doubts.

Measurements and risks

The low-calorie products distributed are produced from approved raw materials under approved conditions and are therefore not considered to pose risks. However, there are known side effects due to weight loss (in brackets: percentage who experienced this); sensitivity to cold (~50%), dry skin (~50%), bad breath (20-30%), fatigue, dizziness, muscle cramps, headache, and gas in the stomach (10-20%), hair loss (0-10%) and gallstones (<5%). In addition, dietary changes can cause stomach upset, which typically subsides within a few weeks. However, there may be risks of which we are currently unaware of. We therefore ask you to let us know if you experience any health problems during the study. Of course, if we discover any side effects that we have not already told you about, you will be informed immediately and the investigator, in consultation with the clinically responsible doctor, will decide whether you can continue in the study.

Simple measurements of the body
Simple measurements of the body, such as weight, height, waist and hip circumference, skinfold thickness, blood pressure and pulse rate are taken using appropriate equipment. These measurements are not expected to cause any risk or discomfort.

Biological material
Mild pain may be experienced at the injection site during blood sampling. In addition, there is a slight risk of swelling and tenderness and a small bruise at the injection site. For blood sampling in children, a local anaesthetic in the form of a plaster or cream is offered. Collection of faeces and urine does not involve any risk or pain as it is collected after natural excretion using the material provided. Breast milk is collected via a pump suitable for the purpose and trained staff will help you. There is no risk and very limited discomfort associated with collection of breast milk. The same is relevant for vaginal swab. There is no risk associated with semen collection.

Questionnaires
Answering of various questionnaires are time consuming but are not expected to cause any risk or discomfort.

With your consent, we will also

Ask permission for the project responsible and project staff to gain access to your patient records and registered information from Sundhed.dk of relevance to your participation in the project and about the planned pregnancy and birth. This is to be able to carry out, monitor, and control the trial. In addition, we will ask for your permission to include your data in the multi-centre project PREPARE CHILD Denmark. We will ask for your permission to contact you by phone annually after the 18-month visit, to collect information about your child's height and weight until the child is 14 years old.

Data handling

All data and other personal information, such as biological material (blood, urine, stool, semen,

vaginal samples, placenta, cord blood and cord tissue and breast milk), that we collect during the study will be treated confidentially and only by persons associated with the study, who are therefore bound by confidentiality. Persons from the authorities that supervise health scientific research trial must have access to all data if they carry out an inspection of the trial. By consenting to participate, you also give permission for these persons to have access to your data. These persons are also subject to confidentiality.

Should you choose to withdraw your consent during the trial, we would like to make you aware that the researchers may include the data already collected in the overall data analysis. Your name will not appear on any material and will instead be assigned a participant number. Likewise, your name will not appear in any reports or other publications of results from this study. Separate from this participant information, you will receive both verbal and written information about the processing and storage of both data and biological materials and biobank.

The data relating to subjects is protected under the Data Protection Act and the General Data Protection Regulation/ GDPR www.retsinformation.dk. The project is registered on statutory registers with the Data Protection Authority.

Research biobank

A research biobank will be set up in the context of the current trial. The purpose is to store biological material from the trial (blood, urine, semen, vaginal, placenta, cord blood and cord tissue, faecal samples and breast milk) until it is analysed and at the latest 10 years after the end of the trial (December 2037). A maximum of 75 ml of blood per participating parent will be collected and stored, as well as a maximum of 4 x 4 x 1 ml urine, 4 x 4 x 1 g faeces, 4 vaginal swabs, 8 x 3 ml placental biopsy samples, 15 ml semen sample and 3 × 30ml breast milk. From your planned baby, 15 ml cord blood and 2 cm cord tissue and a maximum of 44 ml blood, 18 ml urine and 24 g faeces will be collected and stored throughout the study. Collected biological material will be post-processed and stored in the freezer until further analysis. The research biobank is stored at -70°C (or colder) freezers at the Department of Nutrition, Exercise and Sports (NEXS), Frederiksberg C, Hvidovre Hospital or at Rigshospitalet. Biological material will be analysed at NEXS and in other laboratories in Denmark, Europe, USA and Canada. Everything is performed according to the Data Protection Act and the General Data Protection Regulation (GDPR).

Legislation in the US and Canada for processing personal data, including biological material, does not meet all the requirements of the European General Data Protection Regulation (GDPR) and therefore both legal and practical precautions will be taken before your data is shared with laboratories in the US and Canada. The shipping of biological material to USA and Canada will be in comply with the Data Protection Act and the General Data Protection Regulation (GDPR). The biological material will be coded with participant number, study number, and visit number. This means that all samples will be coded and sent in such a way that they cannot be traced back to you without a key, and the key will be kept under special protection and only accessible to authorised personnel. The key will be kept for up to 10 years after the end of the trial (December 2037), after which it will be destroyed.

If you wish to donate any leftover biological material to a biobank for possible future research use, we will ask you to give a separate written consent for this and the transferred biological material will be destroyed within 15 years after

the end of the trial (December 2042). You will receive independent information about the biobank's content, location, how and when material from the biobank may be used in accordance with the law. Leftover of biological material stored for future research will also be in accordance with the Data Protection Act and the General Data Protection Regulation (GDPR). It is entirely voluntary for you to donate your biological material to the biobank and if you do not want this, it does not affect your participation in the trial. If the material is used for future research a new approval must be obtained from the Scientific Ethics Committees of the Capital Region. As a starting point, a new consent form will be obtained but the Committee can make an exemption.

The Research Biobank and the Biobank are registered with the Danish Data Protection Agency and notified to the Scientific Ethics Committees of the Capital Region. The biobank is also registered with the Danish Data Protection Agency.

Insurance and avenues of complaint

You are covered by the Occupational Injuries Insurance Act (cf. LBK no. 977 09/09/2019) in accordance with the insurance conditions in force at the University of Copenhagen. Throughout the project, you will be covered by the Act on Complaints and Compensation in Health Care (cf. LBK no. 995 14/06/2018, www.retsinformation.dk).

Economic circumstances

PREPARE CHILD - CPH is initiated by Associate Professor Nina Geiker, Professor Henriette Svarre Nielsen and Senior Scientist Kristian Almstrup and is funded by the Novo Nordisk Foundation (DKK 16.000.000). The amount for the project is deposited in an independent research account, which is subject to public audit. The funding includes salaries for project staff as well as for project materials and execution. The Toyota-Foundation has sponsored a part of the purchase of an indirect calorimetric system. Pharmovital is sponsoring amino iron for the female participants in the project and PharmaNord is sponsoring folic acid for the women and vitamin D for both female and male participant. When completing the trial, the child will, at the 18 months child follow-up examination, receive a gift of less than DKK 200 which is sponsored by LEGO Charity. The funders have no influence on the execution, interpretation, or publication of the project. None of the project staff have financial associations with the contributors. As a participant, you will not be paid for your participation. The trial products are provided at the Department of Nutrition, Exercise and Sport (NEXS) at no cost to you.

Publications of results

The study is registered on www.clinicaltrials.gov, a database of human clinical studies. The results of the study, whether positive, negative, or inconclusive, will be published in peer-reviewed international journals or at scientific meetings. When the results are published, it will not be possible to identify you in any way.

I you wish to participate in PREPARE CHILD

If you are still interested in participating as participant in the project after reading this participant information, you must attend a non-binding information meeting at the Institute, together with other interested. You can only participate in the project if you have attended an information meeting. At the information meeting, you will receive detailed information about the project and will be offered an interview in a private room with the project staff. Contact us to arrange an information meeting.

If you, after the information meeting, still wish to participate in the project, you must sign a written consent form together with the informing project staff member, and you will be offered a copy of the consent form. You have the right to take consideration time before signing, which does not necessarily have to take place right after the information meeting. By signing, you give your consent to participate in the study and agree to the content and hereby to let your planned child participates in the following child examinations which will be led by medical doctor and professor Henriette Svarre Nielsen, medical doctor and professor Christian Mølgaard, and Associate Professor Camilla Trab Damsgaard. Participation is voluntary and you/your child may withdraw your/their consent at any time without further explanation.

At the information meeting and the examinations, you will meet people employed at NEXS, Hvidovre Hospital and Rigshospitalet who have previously been involved in conducting trials with children. In addition, students may be involved who have been thoroughly trained in the procedures of the trial before participating.

We hope that this information has given you enough insight into what it means to participate in the project, and that you are interested in hearing more at an information meeting. We also ask you to read the attached material "Subject's rights in a health research project" and "Consent form for the processing of personal data and biological material".

If you want to know more

If you wish to participate in PREPARE CHILD - CPH, please contact us for an appointment regarding an information meeting. You are of course also welcome to contact us if you have any further questions or would like more detailed information.

If you have any questions, please **contact** us:

Christian Mølgaad, MD, Professor, PhD
Overall responsible
Department of Nutrition, Exercise and Sports
Rolighedsvej 30
1958 Frederiksberg C

Malene Nygaard, MSc, Cand. Scient
Project manager and daily responsible NEXS
Department of Nutrition, Exercise and Sports
Rolighedsvej 30
1958 Frederiksberg C

Kathrine V. R. Hviid, Doctor
Daily responsible Hvidovre Hospital
Department of Obstetrics and Gynecology
Hvidovre Hospital

tel: +45 51 48 93 80
E-mail: preparechild@nexs.ku.dk.

Best regards,

Responsible for PREPARE CHILD
Christian Mølgaard, Professor, MD,
Department of Nutrition, Exercise and Sports
Rolighedsvej 30
1958 Frederiksberg C

Henriette Svarre Nielsen, MD, Professor, Ph.d.
Recurrent Pregnancy loss Unit
Department of Obstetrics and Gynecology
Hvidovre Hospital
Kettegård Allé 30
2650 Hvidovre

Kristian Almstrup, Senior scientist, MSc, Ph.d.
Department of Growth and Reproduction
Rigshospitalet
Blegdamsvej 9
2100 København Ø

Danish National Center for Ethics, September 2019

The rights of subjects in a health scientific trial

As a participant in a health scientific trial, you should know that:

- Your participation in the trial is entirely voluntary and can only take place after you have received both written and verbal information about the research project and signed the consent form.
- At any time, you can withdraw your consent to participate and withdraw from the trial, orally, in writing or by any other clear means. If you withdraw your consent, this will not affect your right to current or future treatment or any other rights you may have.
- You have the right to bring a family member, friend, or acquaintance to the information meeting.
- You have the right to a take consideration time before signing the consent form.
- Information about your health, other purely private matters, and other confidential information about you which comes to light during the research project is covered by professional secrecy.
- Processing of information about you, including information contained in your blood samples and tissues, will be carried out in accordance with the rules laid down in the Data Protection Act, the General Data Protection Regulation and the Danish Health Care Act. The data controller in the trial must inform you in detail of your rights under the data protection rules.
- It is possible to obtain access to trial protocols in accordance with the provisions of the Public Records Act. This means that you can have access to see all papers relating to the organisation of the trial, except for those parts that contain business secrets or confidential information about others.
- You have the opportunity to complain and obtain compensation according to the rules of the law on complaints and compensation in health care. If an injury should occur during the trial, you can contact the Patienterstatningen (Patient Compensation), see www.patienterstatningen.dk for details.