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Healthy lifestyle before and during pregnancy to prevent childhood obesity: study protocol for a parallel group randomised trial — the PRE-STORK trial

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ABSTRACT

Introduction The global prevalence of people living with overweight has tripled since 1975 and more than 40% of Danish women enter pregnancy being overweight. With the increasing rates of obesity observed in children, adolescents and adults, there is an urgent need for preventive measures. Risk factors for childhood obesity include maternal overweight or obesity before conception and excessive weight gain during pregnancy. Interventions aimed at modifying maternal lifestyle during pregnancy have demonstrated minimal positive or no impact on the health of the children. The 'healthy lifestyle before and during pregnancy to prevent childhood obesity — the PRE-STORK trial' aims to provide insights into the effect of a lifestyle intervention initiated before conception and continued during pregnancy in women with overweight or obesity, on neonatal adiposity in their children.

Methods and analysis In this randomised, two-arm, parallel-group, controlled trial, we will include 360 women with overweight or obesity (aged 18–40; body mass index 25–44 kg/m^2) and their partners. The women will be randomised to receive either standard of care or a lifestyle intervention focused on preconception body weight reduction, regular physical exercise, healthy diet and support from a mentor *before* and *during* pregnancy. The primary outcome is the difference in neonatal adiposity measured in their children at birth. Children conceived during the trial will constitute a birth cohort, monitoring the effects on their health until the age of 18 years.

Ethics and dissemination The trial has been approved by the Regional Committee on Health Research Ethics in the Capital Region of Denmark (identification number H-22011403) and will be conducted in agreement with the Declaration of Helsinki. All results, whether positive, negative and inconclusive, will be disseminated at national or international scientific meetings and in peer-reviewed scientific journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first randomised controlled clinical trial evaluating the effect of prepregnancy-initiated lifestyle intervention on neonatal adiposity and health.
⇒ Establishing a birth cohort with comprehensive preconception health information for families planning pregnancies will provide valuable insights and enhance future knowledge about intergenerational health.
⇒ The results of the present trial may have applicability beyond Denmark and could potentially be included in future clinical guidelines for preconception care.
⇒ Women participating in the standard of care group will be motivated and committed to adopting a healthy lifestyle before pregnancy, which may diminish the estimated effects of the intervention.

Trial registration number ClinicalTrials.gov: NCT05578690 (October 2022).

INTRODUCTION

Obesity affects a variety of bodily functions and increases the risk of diseases such as type 2 diabetes,[1 2] cardiovascular disease,[3] hypertension,[3 4] musculoskeletal disorders,[5] compromised mental health[6] and cancer[7 8] among numerous other factors adversely impacting health. Furthermore, obesity contributes significantly to healthcare costs.[9 10] The global prevalence of people living with overweight or obesity has tripled since 1975 and more than 40% of Danish women enter pregnancy being overweight or obese.[11 12] With the increasing rates of overweight and obesity

observed in children, adolescents and adults, there is an urgent need for preventive measures.[13 14]

Childhood obesity is linked to an increased risk of obesity in adulthood. Adiposity as early as in neonates has been associated with childhood obesity,[15] and children with obesity at the age of 2 years have a high risk of living with obesity later in life.[16–18] Addressing obesity in both childhood and adulthood has posed significant challenges,[19–22] underscoring the importance of preventing obesity from occurring in the next generations.

Preventive measures before conception might be particularly beneficial, as children born to mothers with preconceptional obesity face a threefold higher risk of developing obesity compared to those children born to mothers who do not have obesity.[18 23] Furthermore, maternal obesity before conception and weight gain above the recommended levels during pregnancy are associated with children being born large for gestational age[24–29] as well as epigenetic, metabolic and appetite-regulatory changes linked with childhood obesity.[30–33] Studies in pregnant women with overweight or obesity, exploring the impact of lifestyle interventions focusing on healthy lifestyle during pregnancy, have shown limited effects on adiposity in their children.[34–38] A recent meta-analysis found no significant differences in body weight, length or corresponding z-scores in offspring at 1 month and 7 years of age when comparing lifestyle interventions focusing on healthy lifestyle during pregnancy to standard of care.[39] Importantly, in most of these studies, a lifestyle intervention was initiated after the first trimester of pregnancy. This timing might prove too late to initiate changes affecting child health significantly. Thus, to prevent the development of childhood obesity, interventions may need to be implemented preconceptionally and continue during pregnancy.[23 40]

Only a few studies have explored preconceptional lifestyle interventions addressing maternal and child health.[41–45] The 'Pre-Babe' pilot study showed greater weight loss in the mothers and increased pregnancy chances with a 10-week meal-replacement diet compared with telephone-based dietary advice.[42] The 'FIT-PLESE-study' was a preconception lifestyle intervention for weight loss in women with overweight and infertility, but did not improve birth outcomes or fertility compared with an exercise intervention not aiming at weight loss.[43] However, none of the studies have addressed the impact of a lifestyle intervention before pregnancy on obesity in their children.

In women with overweight or obesity, a reduction in body weight before pregnancy can be achieved with dietary changes, including dietary counselling and low-calorie meal replacement, combined with increased physical activity.[46–51] Both aerobic and resistance exercises enhance energy expenditure and cardiorespiratory fitness, reduce fat mass and maintain muscle mass during weight loss—resistance exercise also improves muscle strength.[52 53] Importantly, previous interventions with structured supervised exercise programmes have proven effective in maintaining healthy weight loss.[19] Further, studies suggest that supportive cognitive-behavioural strategies may increase the likelihood of sustaining lifestyle changes.[54–56] To achieve an intended body weight reduction before pregnancy, followed by weight maintenance and recommended weight gain during pregnancy, we suggest a lifestyle intervention. This lifestyle intervention will involve a combination of a prepregnancy weight reduction based on a low-calorie diet alongside dietary counselling, regular physical exercise and mentor support both before and during pregnancy.

OBJECTIVES

The primary objective of the PRE-STORK trial is to investigate the effect of a lifestyle intervention *before* and *during* pregnancy in women with overweight or obesity on neonatal adiposity measured at birth in their children. The lifestyle intervention involves an intended body weight reduction before pregnancy, dietary counselling, regular physical exercise and support from a mentor aiming at weight maintenance and recommended weight gain during pregnancy compared with standard of care.

METHODS AND ANALYSIS

Participants and recruitment

This trial will include 360 women with overweight or obesity (body mass index (BMI) 25–44 kg/m^2) aged 18–34 years (no previous pregnancy) or aged 18–40 years (previously pregnant >16 weeks) planning a pregnancy within 1 year. Additionally, partners of the randomised women will be offered participation in the trial. Detailed inclusion and exclusion criteria are listed in box 1. Participants will be recruited from the Capital Region and Region Zealand of Denmark via local newspapers, online media, flyers, general practitioners, hospital and private physicians and health nurses.

Trial design and timeline

The PRE-STORK trial is a single-centre, randomised (1:1 ratio), parallel-group, controlled trial. The study is registered at www.clinicaltrials.gov (NCT05578690) and was approved by the Scientific Ethical Committee of the Capital Region of Denmark on 9 September 2022 (approval number H-22011403) (see table 1). The primary place of study execution and data collection is Steno Diabetes Center Copenhagen, Borgmester Ib Juuls Vej 83, DK-2730 Herlev, Denmark.

The timeline for participation is illustrated in figure 1, and an overview of assessments performed is provided in table 2. After thorough information and screening by telephone, all potentially eligible participants will attend a screening visit (V0) to assess eligibility criteria. Before accepting participation in the study, the woman will give informed consent orally and in writing. If a woman meets the inclusion criteria, a baseline visit (V1) will be conducted, after which the woman will be randomised.

Box 1 Eligibility criteria

Women inclusion criteria

BMI 25–44 kg/m^2. Age 18–34 years (no previous pregnancy) or 18–40 years (previously pregnant >16 weeks). Planning a pregnancy within the next year. Willingness to lose at least 10% of initial body weight before pregnancy and be physically able to adhere to the WHO physical activity recommendations when entering the study. Willing to postpone pregnancy until at least 6 months after randomisation. Planning antenatal care and delivery at Herlev Hospital. Danish or English speaking.

Women exclusion criteria

Diabetes (FPG >7 mmol/L and HbA1c ≥48 mmol/mol). Previous GDM treated with insulin during pregnancy. PCOS treated with metformin. Treatment with medication which significantly affect glucose metabolism, appetite or energy balance. The use of medications that cause clinically significant weight gain or loss. Habitual abortion (more than three abortions in a row). Known infertility (defined as fertility treatment and/or no obtained conception with the same partner after trying >12 months). Previous bariatric surgery. Significant psychiatric disorders. Uncontrolled/severe medical issues including cardiovascular, pulmonary, rheumatologic, haematologic, oncologic, infectious or endocrine disease. Regular exercise training at high intensity (eg, spinning) >3 hours per week. Known eating disorder.

Partner inclusion and exclusion criteria

There are no inclusion or exclusion criteria for the partner.

BMI, body mass index; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HbA1c, glycated haemoglobin; PCOS, polycystic ovarian syndrome.

After an initial 8-week low-calorie diet, women in the intervention group will attend a visit (V2). All women will attend visits every 6 months until pregnancy or 2 years of participation (V3, V4a and V4b). Both groups will have four visits during pregnancy at pregnancy weeks 11–14, 18–21, 24–28 and 34 (V5, V6, V7 and V8), one visit at the time of birth (V9) and a final visit 3 months after birth (V10). All partners of enrolled women will be offered examinations at baseline (V1), 6 months after baseline (V3), at the time of pregnancy (V5) and at the end of the trial (V10).

Women in the intervention group who become pregnant before visit 3 (within 6 months of participation) will not be excluded from the study. If pregnancy occurs earlier than expected, the woman will be invited to attend the scheduled pregnancy visits.

A woman may be withdrawn from the trial at the discretion of the investigator due to a safety concern. This is an intention-to-treat study, and therefore, participants are retained in the study regardless of adherence levels or the emergence of new medical conditions. Withdrawn women will not be replaced. However, rescreening within the recruitment period is allowed at the investigator's discretion. Women (and children) lost to follow-up will be followed by their social security number through the Danish registries and via their electronic medical records.

Intervention

The PRE-STORK lifestyle intervention consists of three main components: a dietary, a physical exercise and a mentorship component. The intervention is divided into four phases, with no active intervention in phase 4 (figure 1). The standard of care group will not receive any active intervention but will be advised to consult their general practitioner for guidance on addressing prepregnancy obesity according to current guidelines. Further information regarding the standard of care for women with overweight or obesity before and during pregnancy can be found in the section 'Standard of Care'. Partners in the intervention group will be encouraged to participate in workshops, attend consultations with dietitians and engage in regular physical exercise. If the BMI of partners exceeds 27 kg/m^2, they will additionally be encouraged to follow the first phase of the dietary intervention, including a very low-calorie diet.

Diet

The initial objective of the dietary intervention is to achieve weight loss, followed by a shift towards a diet focused on body weight maintenance. Throughout the study duration, the dietary intervention will be tailored individually for each woman, aligning with current guidelines and recommendations.[57 58] All women will complete dietary registrations at visit 1, visit 3, visit 7 and visit 10. These data will be used for ongoing evaluation of their dietary habits and serve as a foundation for pinpointing areas to enhace the dietary intervention towards healthier and more sustainable dietary habits.

Phase 1 involves an 8-week very low-calorie diet with meal replacements (800 kcal/day), aiming to achieve a weight loss of at least 10%. Women will have individual consultations with a dietitian for dietary assessment and information before initiating the low-calorie diet. To increase adherence in phase 1, women will be offered six group sessions supervised by a dietitian, focusing on challenges, barriers to following the diet, and inspiration for meal preparation. Following the completion of the low-calorie diet, individual sessions with a dietitian will ensure proper food reintroduction and provide guidance on sustained body weight maintenance through diet. If further weight loss is targeted or if the initial 10% weight loss goal has not been achieved in phase 1, a calorie-restricted diet with a deficit of 500 kcal/day will be initiated.

Phase 2 continues until pregnancy is achieved or until the end of the study. Initially, there will be a gradual transition, closely monitored by dietitians, from a diet solely comprised of meal replacements to a normal full diet. Following this, monthly group sessions and individual consultations with dietitians will be conducted to guarantee ongoing adherence to the diet, aligning with general recommendations.[57] The frequency of meetings and the content of guidance will be tailored to each woman's preferences and planned individually. Additionally, cooking classes with emphasis on meals rich in vegetables, fibres and whole grains, and low in fat, are provided along with lectures, diet plans and recipes incorporating dietary recommendations.

Table 1 Trial registration data

Data category	Information
Primary registry and trial identifying number	H-22011403
Date of registration in primary registry	29 September 2022
Secondary identifying numbers	None
Source(s) of monetary or material support	Novo Nordisk Foundation
Primary sponsor	Novo Nordisk Foundation
Secondary sponsor(s)	Clinical and Translational Research, Steno Diabetes Center Copenhagen, Herlev, Denmark
Contact for public queries	TV (e-mail: tina.vilsboell.01@regionh.dk) SST (e-mail: torekov@sund.ku.dk) LGG (e-mail: louise.groth.grunnet.02@regionh.dk)
Contact for scientific queries	TV (Clinical Research, Steno Diabetes Center Copenhagen, Borgmester Ib Juuls Vej 83, DK-2730 Herlev, Denmark; phone: +45 40940825; email: tina.vilsboell.01@regionh.dk) SST (University of Copenhagen; phone: +4522983827 email: torekov@sund.ku.dk) LGG (Clinical Research, Steno Diabetes Centre Copenhagen; Borgmester Ib Juuls Vej 83, DK-2730 Herlev, Denmark; phone: +4560671704; email: louise.groth.grunnet.02@regionh.dk)
Public title	Healthy lifestyle before and during pregnancy to prevent childhood obesity: study protocol for a parallel group randomised trial — The PRE-STORK trial
Scientific title	Healthy lifestyle before and during pregnancy to prevent childhood obesity: study protocol for a parallel group randomised trial — The PRE-STORK trial
Countries of recruitment	Denmark
Health condition(s) or problem(s) studied	The effect of a lifestyle intervention before and during pregnancy on neonatal adiposity, measured at birth in children of women with overweight or obesity.
Intervention(s)	Treatment group: a lifestyle intervention involving an intended body weight reduction before pregnancy, dietary counselling, regular physical exercise and support from a mentor aiming at weight maintenance and recommended weight gain during pregnancy.
	Control group: standard of care
Key inclusion and exclusion criteria	► Ages eligible for study: age 18–34 years (no previous pregnancy) or 18–40 years (previously pregnant >16 weeks) ► Sexes eligible for study: women and their partners ► Accepts healthy volunteers: no
	Inclusion criteria: ► BMI 25–44 kg/m^2 ► Planning a pregnancy within the next year ► Willingness to lose at least 10% of initial body weight before pregnancy and be physically able to adhere to the WHO physical activity recommendations when entering the study ► Willing to postpone pregnancy until at least 6 months after randomisation ► Planning antenatal care and delivery at Herlev Hospital ► Danish or English speaking
	Exclusion criteria: ► Diabetes (FPG >7 mmol/L and HbA1c ≥48 mmol/mol) ► Previous GDM treated with insulin during pregnancy ► PCOS treated with metformin ► Treatment with medication which significantly affects glucose metabolism, appetite or energy balance ► The use of medications that cause clinically significant weight gain or loss ► Habitual abortion (more than three abortions in a row) ► Known infertility (defined as fertility treatment and/or no obtained conception with the same partner after trying >12 months) ► Previous bariatric surgery ► Significant psychiatric disorders ► Uncontrolled/severe medical issues including cardiovascular, pulmonary, rheumatologic, haematologic, oncologic, infectious or endocrine disease ► Regular exercise training at a high intensity (eg, spinning) >3 hours per week ► Known eating disorder
Study type	Interventional
	Allocation: randomised 1:1, two-arm, parallel-group, controlled trial
	Primary purpose: prevention of childhood obesity
Date of first enrolment	26 October 2022
Target sample size	360 women

Continued

Table 1 Continued

Data category	Information
Recruitment status	Recruiting
Primary outcome(s)	Difference in neonatal adiposity between groups, measured as total fat mass in grams at birth or up to 72 hours post partum by paediatric air displacement plethysmography (PEA POD)

BMI, body mass index; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HbA1c, glycated haemoglobin; PCOS, polycystic ovarian syndrome; PEA POD, paediatric air displacement plethysmography.

Phase 3 begins when the woman becomes pregnant and continues until birth. This phase involves regular consultations with a dietitian tailored to the woman's specific needs. During this phase, the woman will receive guidance on maintaining healthy eating habits during pregnancy and achieving the recommended pregnancy weight gain.[58]

Physical exercise

Throughout the intervention, women will be encouraged to adhere to the WHO guidelines for healthy individuals recommending at least 150 min per week of moderate-intensity exercise (64%–76% of maximal heart rate), or 75 min per week of vigorous-intensity (77%–95% of maximal heart rate) or a combination.[59 60] The women will be encouraged to adhere to these recommendations by participating in 1-hour supervised exercise sessions at the study location twice a week and engaging in moderate-to-vigorous-intensity exercise individually at least once per week. The supervised exercise will consist of a combination of vigorous-intensity, interval-based indoor cycling and circuit whole-body strength training. For exercise done independently, an exercise programme combining aerobic exercise and circuit training with functional strength exercises is provided each week. To offer flexibility and accommodate exercise preferences, participants will have access to workout videos, outdoor training sessions and live online workout sessions tailored to their individual needs. Dialogue-based educational workshops will be conducted regularly, focusing on exercise during pregnancy and methods for maintaining motivation in training regimens. Participants will wear exercise watches with heart rate monitors (Garmin Forerunner 55, Garmin, Olathe, Kansas, USA) throughout the study period to collect data on exercise sessions (supervised and unsupervised), daily physical activity measured as steps per day, and sleep. This data will aid in assessing adherence to the weekly criteria of exercise volume and offer continuous feedback to the participants regarding their training progress. Regular follow-ups every 2 weeks will be conducted to support the participants in maintaining their exercise routines and adjusting the exercise plan as necessary.

Phase 1 involves conducting VO^2 peak test and measuring of peak heart rate during exercise for all women before the initiation of the intervention. Throughout the 8-week low-calorie diet, women will be advised to participate in supervised exercise sessions consisting of 30 min aerobic interval-based cycling aiming for 75%–80% of maximum heart rate and 30 min of progressive machine-based strength training at moderate-to-vigorous intensity (5–12 repetition maximum). Additionally, the women will be advised to perform a 1-hour brisk walk once weekly during this phase.

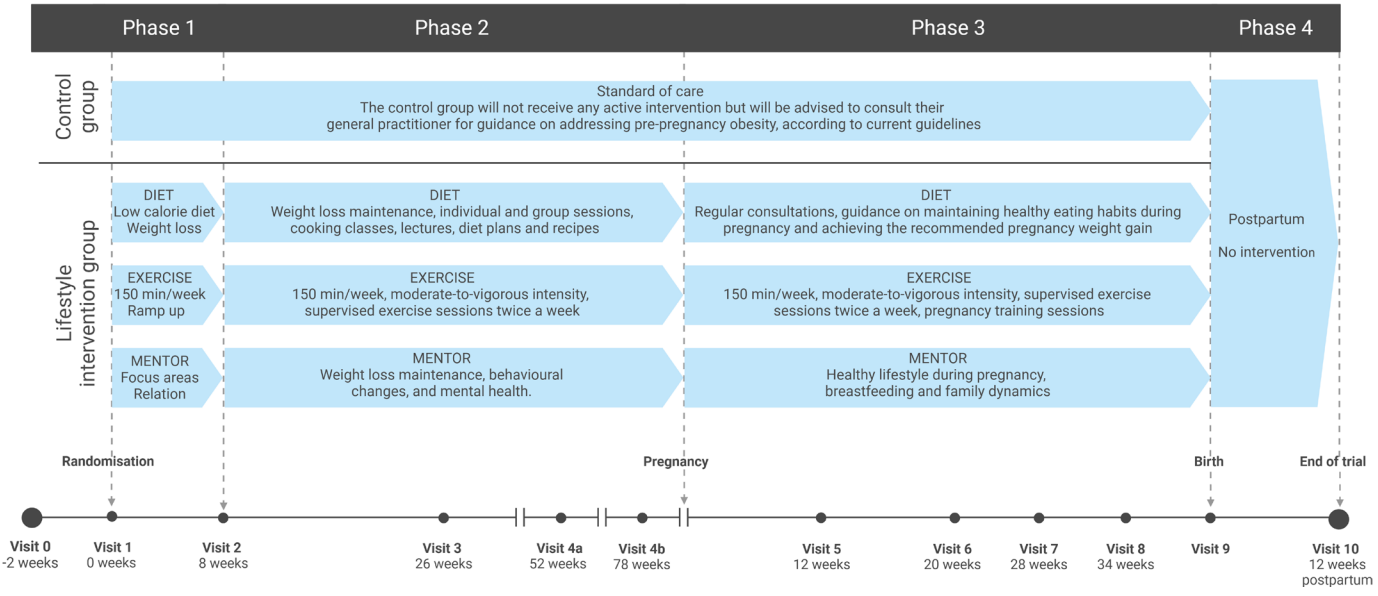

Figure 1 Timeline.

Table 2 Overview of study visits and corresponding examinations

	Screening	Randomisation	Before pregnancy				Pregnancy				Birth	Post partum
Visits	V0	V1	V2	V3	V4a	V4b	V5	V6	V7	V8	V9	V10
Timing of visit (weeks)	–2	0	8	26	52	78	11–14	18–21	24–28	34	0	12
Visits intervention group	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Visits control group	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient-related outcomes												
Informed consent	X											
Inclusion/exclusion criteria	X											
Pregnancy test	X	X	X	X	X	X						X
Efficacy outcomes (maternal)												
Height	X											
Body weight	X	X	X	X	X	X	X	X	X	X		X
Waist/hip circumference		X	X	X	X	X						X
Blood pressure	X	X	X	X	X	X	X	X	X	X		X
Body composition(DXA scan)		X		X								X
Body composition (bioimpedance)		X	X	X	X	X	X	X	X	X		X
Fasting blood samples		X	X	X	X	X	X	X	X	X		X
Food registration		X		X					X			X
Indirect calorimetry		X		X								X
Fibro-Scan		X		X					X			X
Accelerometer		X		X					X			X
Exercise test		X		X								X
CGM									X			
OGTT									X			
SBFPT		X		X					X			X
Urine		X		X					X			X
Faeces		X		X					X			X
Efficacy outcomes (fetal/infant)												
Fetal weight and biometrics								X	X	X		
Meconium/faeces										X		X
Cerebral media/umbilical artery function									X	X		
Apgar score										X		
Infant body composition										X		X

Continued

Table 2 Continued

	Screening	Randomisation	Before pregnancy	Pregnancy	Birth	Post partum
Baby body weight and length					X	X
Placenta biopsy+cord blood					X	
Heel prick test/blood sample					X	X
Echocardiography					X	X
Standard electrocardiography					X	X
Breast milk sample					X	X
Partner outcomes						
Body weight+height		X	X	X		X
Waist/hip ratio		X	X	X		X
Blood pressure		X	X	X		X
Body composition (bioimpedance)		X	X	X		X
Fasting blood samples		X	X	X		X
Semen sample		X	X	X		
Urine		X	X			X
Questionnaires						
Short Form 36-Item Health Survey (SF-36)		X	X	X		X
International Physical Activity Questionnaire (IPAQ)		X	X	X		X
Pittsburgh Sleep Quality Index (PSQI)		X	X	X		X
Three-factor eating questionnaire (TFEQ)		X	X	X		X
Control of Eating Questionnaire (CoEQ)		X	X	X		X
Social Support on Eating and Exercise Habits		X	X	X		X
Rosenberg Self-Esteem Scale (RSES)		X	X	X		X
General Self-Efficacy Scale (GSES)		X	X	X		X
Weight Bias Internalization Scale (WBIS)		X	X	X		X
Major Depression Inventory (MDI)		X	X	X		X
General Anxiety Disorder 7-item (GAD-7)		X	X	X		X
Perceived Stress Scale (PSS)		X	X	X		X
Edinburgh Postnatal Depression Scale						X
Breastfeeding practices						X

BMI, body mass index; CGM, continuous glucose monitoring; DXA, dual X-ray absorptiometry; OGTT, oral glucose tolerance test; SBFPT, Steno biometric food preference test.

Phase 2 will focus on sustaining the exercise routine and increasing the exercise intensity to achieve weight maintenance. Women will continue to participate in supervised exercise sessions and engage in physical activity on their own to reach the weekly exercise volume. Both supervised exercise and unsupervised will consist of 30 min of aerobic interval training aiming at 80%–85% of maximum heart rate and 30 min of functional strength exercises. Furthermore, to improve understanding and ensure consistent performance throughout pregnancy, women will be instructed in pelvic floor muscle exercises aimed at preventing urinary incontinence postpartum.[61]

Phase 3 aims to maintain a consistent level of moderate-to-vigorous-intensity exercise throughout pregnancy, combining aerobic and strength training including pelvic floor muscle exercise. Exercise group sessions will be available for pregnant women, along with individual exercise programmes tailored to address any limitations related to pregnancy. The exercise protocol will adhere to established guidelines and be tailored to individual needs, considering current health status, any concurrent health conditions and potential complications arising during pregnancy.[62]

Mentor

A mentor will be assigned to each woman to assist them in action planning and goal setting, offer feedback and provide support when faced with obstacles. The aim of this programme is to enhance the woman's motivation, support, health literacy, skills and self-efficacy, hopefully leading to improved self-esteem, better mental health and reduced stress, depression and anxiety.

In the context of the PRE-STORK trial, a conversation wheel has been developed, drawing from existing literature,[63] insights from previous studies[64] and behavioural theory.[65] This interactive tool serves as a foundation for discussions, allowing participants to guide the conversation towards areas they prioritise. Mentors will assist participants in setting realistic and positive goals, involving partners and networks as desired, to foster social support.

All mentors possess a professional healthcare background and have undergone training conducted by psychologists specialising in overweight and eating disorders before initiating their mentoring sessions. Additionally, mentors participate in regular monthly supervision with a qualified psychologist, providing them with opportunities to receive feedback and acquire additional tools for effectively supporting the women. All interactions, including detailed documentation of discussions, are systematically recorded in Research Electronic Data Capture (REDCap).

Phase 1 focuses on establishing an optimal long-term relationship between mentor and mentee and outlining the participants' focus areas.

Phase 2 includes regular individual meetings tailored to the participants' needs and workshops centred on building relationships, understanding health perceptions, and coping with living with overweight. Lecture sessions are offered covering topics such as weight loss maintenance, behavioural changes and mental health. The mentor will focus thoroughly on supporting and encouraging the women in sustaining healthy habits to enhance weight maintenance.

Phase 3 addresses the challenges and barriers associated with maintaining a healthy lifestyle during pregnancy, including considerations related to breastfeeding and family dynamics. Meeting frequency and content will be adjusted to meet individual needs.

Preventing discontinuation and safety measures

Given the extensive nature of the intervention and the significant time commitment required from the women, we will implement a series of measures to prevent dropout and improve adherence to the intervention. Every 2 weeks, women will be requested by email to complete an online self-assessment questionnaire assessing their level of motivation and overall well-being in terms of physical activity, diet, sleep, stress, mood and motivation. This questionnaire serves as a reflective tool designed to help women identify areas posing challenges to their adherence to the intervention. If a woman indicates, based on predefined criteria, that she has encountered difficulties, she will be offered a session with her mentor to discuss how support and guidance can be provided to ensure her safety and enhance her adherence.

The exercise watches worn throughout the intervention offer immediate and continuous feedback on weekly exercise duration and intensity. This feedback assists in identifying women encountering difficulties in adhering to the weekly exercise guidelines. Women are encouraged to stay informed about their weekly training progress. If they have difficulties meeting the recommendations, they are offered a motivational session with a trainer to individualise the exercise plan and adjust physical activity behaviour.

Women are encouraged to attend weekly weigh-in sessions. Weighing will occur in a private setting, with only one study staff member present. Participation in the weigh-in is voluntary, and women have the option to be weighed without knowing their weight. Regular weigh-ins enable women to track their weight progress and reflect on behaviour changes under the support of a mentor.

Throughout the intervention, women are encouraged to reach out to relevant personnel if any issues arise, and they can always request additional sessions with a mentor, dietitian or trainer.

Adverse events are routinely collected throughout the trial period and evaluated by a physician. If there is suspicion that a woman has developed a serious adverse event, this will be evaluated by a multidisciplinary team of specialists in obstetrics and endocrinology. A plan for subsequent treatment, reporting and study participation will be developed accordingly. If the woman has developed an adverse psychological reaction during the trial, this will be assessed by a physician, and the woman will be referred to her primary care provider for further

evaluation and treatment if deemed necessary. Additionally, women complete the Major Depressive Inventory Questionnaire at the 6-month follow-up (visit 3), at 28 weeks of pregnancy (visit 7), and 3 months after birth (visit 10). If a woman shows signs of depression, she is advised to consult her general practitioner for further evaluation.

Standard of care

In Denmark, routine standard of prenatal care includes three consultations with a general practitioner at gestational weeks 6–10, 25 and 32, during which maternal weight is recorded. Women are advised to engage in 30 min of physical activity daily and guidance on the recommended weight gain during pregnancy is provided, based on the guidelines issued by the Danish Health Authority.[66] Additionally, women with a BMI over 35 kg/m² are offered a consultation with an obstetrician during pregnancy.

Endpoints

The primary endpoint is the difference in neonatal adiposity between groups, measured as total fat mass in grams at birth or up to 72 hours post partum by paediatric air displacement plethysmography (PEA POD).[67–70] Additionally, secondary endpoints, tertiary exploratory endpoints and descriptive outcomes will be assessed for women, partners and children. For a comprehensive overview of these, see box 2 . All endpoints will be evaluated in the intention-to-treat population. Tertiary explanatory endpoints include outcomes with unknown clinical consequences that, nevertheless, may contribute to our understanding and explain primary and secondary endpoints.

Outcome assessments

For an overview of all assessments and respective time points, see table 2.

Anthropometrics, body composition, blood pressure and heart rate

Body weight and body composition will be measured by bioimpedance without shoes and wearing light clothes on the Medical Body Composition Analyser (seca 515/514, Hamburg, Germany).[71] Dual-energy X-ray absorptiometry (DXA) (Lunar iDXA, GE Medical Systems, Waukesha, Wisconsin) scans will be performed in a fasting state to measure body fat mass, fat-free mass, and bone density.[72] Height will be measured using an ultrasonic height measurement (seca 257, Hamburg, Germany) to the nearest 0.1 cm.[73] Waist circumference, measured at the midpoint between the lowest rib and the iliac crest, and hip circumference, measured at the level of the great trochanters, will be measured in duplicate to the nearest 0.1 cm after gentle expiration. If the difference between the initial duplicate measures is more than 0.5 cm, a third measure will be performed. Blood pressure and resting heart rate will be measured in a sitting position three times with 2-min intervals after a 10-min rest.

Box 2 Secondary endpoints, tertiary exploratory endpoints and descriptive outcomes

Secondary endpoints (fetal and infant) (between group difference)

Fetal and infant body weight, abdominal circumference, femur length and head circumference assessed during pregnancy (week 18–21, 24–28 and 34), at birth and 3 months after birth. Infant BMI z-score assessed at birth and 3 months after birth. Infant body fat mass (g), fat-free mass (g) and fat percentage measured by PEA POD assessed 3 months after birth. Infant body composition assessed 3 months after birth measured by DXA. Gestational age at birth. Weight for gestational age birth. Proportions of infants being born LGA and SGA. Apgar score assessed as the proportions of infants born with Apgar score <7. Changes in faecal microbiota composition assessed at birth and 3 months after birth. Cardiac function and cardiac structure assessed by echocardiography assessed at birth and 3 months after birth. Placenta function assessed by the weight of the placenta (in gram). Placenta function assessed during pregnancy (week 28 and 34) measured by the amount of amniotic fluid, cerebral media and umbilical artery Doppler flow of the foetus.

Secondary endpoints (women) (between group difference)

Proportion of women who achieve a weight loss of ≥10% at the time of pregnancy or 2 years after randomisation without achieving pregnancy. Proportion of women without obtaining pregnancy or live-born offspring within a period of 2 years. Oral glucose tolerance during (OGTT) assessed in pregnancy (week 24–28) evaluated by: maximum observed glucose concentration, time to maximum observed glucose concentration and baseline-subtracted area under the plasma glucose concentration time curve (0–120 min). Fasting insulin assessed during pregnancy (week 24-28). Insulin resistance during OGTT assessed in pregnancy (week 24–28) evaluated by: area under the insulin concentration time curve (0–60 min and 0–120 min), maximum observed insulin concentration, time to maximum observed insulin concentration and baseline-subtracted area under the insulin concentration time curve (0–60 min and 0–120 min). Hormonal response during OGTT for glucagon, GLP-1, PYY, GIP and ghrelin assessed during pregnancy (week 24–28). Glycaemic variability assessed during pregnancy (week 24–28) measured by CGM and during OGTT. Body weight, height and BMI assessed prior to pregnancy (baseline, 6 months and 12 months), during pregnancy (week 11–14, 18–21, 24–28 and 34) and 3 months after giving birth. Body composition (fat percent and muscle mass percent) assessed prior to pregnancy (baseline, 6 months and 12 months), during pregnancy (week 11–14, 18–21, 24–28 and 34) and 3 months after giving birth. Body composition measured by DXA prior to and after pregnancy. During pregnancy measured by bioelectrical impedance analysis. Bone density (T-score) assessed prior to pregnancy (baseline, 6 months and 12 months) and 3 months after giving birth by DXA. Resting blood pressure and resting heart rate assessed prior to pregnancy (baseline, 6 months and 12 months), during pregnancy (week 11–14, 18–21, 24–28 and 34) and 3 months after giving birth. Fasting plasma glucose, HbA1c and lipid profile (cholesterol, HDL, LDL, VLDL, TG, ApoA/ApoB ratio) assessed prior to pregnancy (baseline and 6 months) during pregnancy (week 24–28) and 3 months after giving birth. Liver fat and stiffness assessed by Fibro-Scan® prior to pregnancy (baseline and 6 months), during pregnancy (week 24–28) and 3 months after giving birth. Food preference assessed by SBFPT prior to pregnancy (baseline and 6 months), during pregnancy (week 24–28) and 3 months after giving birth. Bone homeostasis derived from bone turnover markers CTX, P1NP and OC assessed prior to pregnancy (baseline and

Continued

Box 2 Continued

6 months), during pregnancy (week 24–28) and 3 months after giving birth. Inflammatory markers hs-CRP, TNFα, IL-6 and LBP assessed prior to pregnancy (baseline and 6 months), during pregnancy (week 24–28) and 3 months after giving birth. Waist and hip circumference assessed prior to pregnancy (baseline, 8 weeks, 6 months, 12 months and 18 months) and 3 months after giving birth. Resting energy expenditure using indirect calorimetry assessed prior to pregnancy (baseline and 6 months) and 3 months after giving birth. Exercise capacity measured by maximal exercise test assessed prior to pregnancy (baseline and 6 months) and 3 months after giving birth. Proportion of women with prediabetes assessed prior to pregnancy (baseline and 6 months).

Tertiary exploratory endpoint (partners) (between group difference)

Body weight, height and BMI assessed prior to pregnancy of the woman (baseline and 6 months), during pregnancy (week 11–14) and 3 months after birth. Body composition by bioelectrical impedance analysis (fat mass, fat free mass, fat percentage) assessed prior to pregnancy of the woman (baseline and 6 months), during pregnancy (week 11–14) and 3 months after birth. Resting blood pressure and resting heart rate assessed prior to pregnancy of the woman (baseline and 6 months), during pregnancy (week 11–14) and 3 months after birth Semen quality and epigenetic profile of sperm cells assessed prior to pregnancy of the woman (baseline) and during pregnancy (week 11–14).

Tertiary exploratory endpoint and descriptive outcomes (infants, women and partners) (between group difference)

Proportion of women who initiate fertility treatment during the trial period. Appetite, physical activity, wellbeing, sleep, self-perception of body weight, self-esteem, and partner support based on questionnaires (women and partner) assessed prior to pregnancy (baseline and 6 months), during pregnancy (week 24–28) and 3 months after birth. Epigenetic profile in peripheral blood mononuclear cells (women, partner and child). Epigenetic profile from umbilical cord blood and placenta biopsies assessed at birth. Changes in faecal microbiota composition (women) assessed prior to pregnancy (baseline and 6 months), during pregnancy (week 24–28) and 3 months after birth. Changes in faecal microbiota composition (infant) assessed prior at birth and 3 months after birth. Associations between parent and child genetics and obesity-related phenotypes assessed at the end of the trial. Proportion of women who experience complications during delivery (premature delivery, labour induction, vacuum extraction, shoulder dystocia, planned and emergency caesarean section, postpartum haemorrhage >1000 ml and stillbirth). Proportion of children with neonatal complications including asphyxia, hypoglycaemia, jaundice and admittance to neonatal intensive care.

ApoA/ApoB, apolipoprotein B/apolipoprotein A1 ratio; BMI, Body mass index; CGM, continuous glucose monitoring; CTX, carboxy-terminal collagen crosslinks; DXA, dual X-ray absorptiometry; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LBP, lipopolysaccharide-binding protein; LDL, low-density lipoprotein; LGA, large for gestational age; OC, osteocalcin; OGTT, oral glucose tolerance test; PEA POD, paediatric air displacement plethysmography; PYY, peptide tyrosine; P1NP, type 1 amino-terminal pro-peptide; SBFPT, steno biometric food preference task; SGA, small for gestational age; TG, triglycerides; TNF-α, tumour necrosis factor-α; VLDL, very-low-density lipoprotein.

Blood samples, faeces, urine, semen and breast milk

A research biobank will be established to store blood, urine, semen, faeces samples and breast milk (when relevant) from participants. For women and partners, blood samples in the fasted state will be collected. For children, blood samples will not be collected in the fasted state. Blood samples will be used for the assessment of biomarkers of general and metabolic health, lipid profile, liver function, bone turnover markers, kidney function, fertility status and sex hormones, appetite hormones, coagulation status and immune markers. Faecal samples will be collected to investigate faecal bacterial composition. For women and partners, midstream urine samples will be collected and analysed for protein, glucose, leucocytes, erythrocytes, pH, ketones and human choriogonadotropin. Semen will be collected to investigate epigenetics of the spermatozoa. Breast milk will be collected from women who are breastfeeding. Breast milk samples will be obtained in the fasted state, before the initial morning feed and at least 2 hours after the preceding feed. A complete extraction of milk from one breast will be collected. Whole milk samples and skimmed milk samples will be collected and stored at −80°C for later analyses.

Exercise watches and accelerometer

A 3-axis accelerometer device (AX3, Axivity, Newcastle, UK) will be worn on the thigh and on the lower back seven consecutive days to assess habitual physical activity and sleep duration.[74] Women in the intervention group will be given an exercise watch (Garmin forerunner 55, Garmin, Olathe, Kansas, USA) to obtain data on physical activity and sleep patterns throughout the trial.

Oral glucose tolerance test (OGTT)

At gestational age 24–28 weeks, all women will undergo a 2-hour 75 g OGTT to assess glucose tolerance. During the test, blood samples will be systematically collected at specific time intervals following glucose ingestion: 0 min, 15 min, 30 min, 45 min, 60 min, 90 min and 120 min. Each time point will allow for the assessment of hormonal changes associated with glucose metabolism and appetite regulation. If the woman meets the current diagnostic criteria for gestational diabetes mellitus or the test results requires further follow-up,[75] she will be referred to appropriate treatment at the Obstetrical Department.

Indirect calorimetry

Resting energy expenditure will be assessed over a 30-min resting period through indirect calorimetry in the fasted state, using the Vyntus CPX Canopy (CareFusion, Hoechberg, Germany) ventilated hood system and Sentry Suite software. Calibration will be conducted in adherence to guidelines before each testing session.[76] The respiratory exchange ratio, derived from the correlation between oxygen consumption and carbon dioxide production, will serve as an indicator of the proportional contributions of carbohydrate and fat oxidation.[76 77]

Continuous glucose monitoring

Continuous glucose monitoring (CGM) will be facilitated using the Dexcom G7 (Dexcom, San Diego, California, USA).[78] The Dexcom G7 CGM sensor measures

interstitial glucose concentrations every 5 min without any need for calibration. The CGM will be attached to the back of the upper dominant arm according to the Dexcom G7 user manual. All glucose data will be transmitted using the Dexcom Clarity software. The sensor will measure for 10 days.

Fibroscan

To assess hepatic fibrosis and steatosis, an ultrasound using a FibroScan (Echosens, Paris, France) will be conducted in all women. FibroScan is a simple, validated, reliable and safe non-invasive method for assessing hepatic fibrosis and steatosis.[79]

Maximal exercise test

Participants will undergo a maximal physical performance cardiopulmonary exercise test to evaluate peak oxygen uptake. The test will be conducted on an electromagnetically braked cycle ergometer (Lode Corival cpet, Groningen, Netherlands) with continuous monitoring of oxygen uptake and carbon dioxide excretion, using an automated online system (Vyntus CPX, CareFusion, Hoechberg, Germany).[80] The heart rate will be monitored with a Polar H10 heart rate monitor (Polar Electro Oy, Kempele, Finland) during the entire test. After a 3-min warm-up period (25 Watt), a ramp test with a progressively increasing workload continues until voluntary exhaustion. The protocol is adjusted to the participant's expected physical fitness level. The test is accepted when at least two out of three parameters are met: plateau in oxygen consumption despite increased workload, respiratory exchange ratio above 1.15, or reaching the age-predicted maximal heart rate (220 minus the participant's age in years).[81]

Steno biometric food preference task

Food preference will be examined by using the steno biometric food preference task, a computer-based test that combines measures from the Leeds Food Preference Questionnaire with biometric measures from eye tracking.[82]

Dietary registration

Participants will be instructed to document their dietary intake over two weekdays and two weekend days, with weighing of all food items and beverages accurate to 1 g.[83] Intake of macronutrients, micronutrients and energy will be calculated using the software package Vitakost (Vitakost, Kolding, Denmark).

Questionnaires

Participants will be requested to complete the subsequent questionnaires: Short Form 36-Item Health Survey (SF-36),[84] The International Physical Activity Questionnaire (IPAQ),[85] the Pittsburgh Sleep Quality Index (PSQI),[86] Three-Factor Eating Questionnaire (TFEQ),[87] Control of Eating Questionnaire (CoEQ),[88] Social Support on Eating and Exercise Habits,[89] Rosenberg Self-Esteem Scale (RSES),[90] General Self-Efficacy Scale (GSES),[91] Weight Bias Internalization Scale (WBIS),[92] Major Depression Inventory (MDI),[93 94] General Anxiety Disorder 7-item (GAD-7),[95] Perceived Stress Scale (PSS),[96] Breastfeeding Practices[97] and Edinburgh Postnatal Depression Scale.[98]

Fetal measurements

Fetal weight, fetal biometrics (abdominal circumference, femur length, biparietal diameter and occipito-frontal diameter), fetal blood flows (a. cerebri media, a. umbilicus) and the amount of amniotic fluid will be estimated by two-dimensional ultrasound examinations performed on ultrasound scanners from GE Healthcare (Buckinghamshire, UK) at gestational age 26 to 28 weeks and 32 to 34 weeks.[99] Additionally, data from the Danish routine ultrasound screening programme at gestational ages 11 to 14 weeks and 18 to 21 weeks will be collected.[100]

Umbilical cord blood sample and placenta biopsies

Umbilical cord blood samples will be collected in serum clot activator tubes, dipotassium ethylenediaminetetraacetic acid tubes, and coagulation sodium citrate tubes from the large veins at the base of the cord on the placenta, or from the veins within the cord itself.[101] The placentas will be macroscopically examined for signs of disrupted development and processed within 30 min after delivery. After removal of the cord and the amnion, the placenta will be weighed. Biopsies will be collected from each quadrant and divided into the maternal and fetal side. Biopsies will be stored at −80°C for later analyses.[102 103]

Paediatric air displacement plethysmography

In the children, body weight, fat mass and fat-free mass will be measured using PEA POD (Cosmed, Rome, Italy).[69 70]

Transthoracic echocardiographic (children)

Transthoracic echocardiographic examinations will be performed following the protocol for the Copenhagen Baby Heart Study.[101] Using Vivid E9 ultrasound equipment (General Electric, Horten, Norway), standard subxiphoid, apical, left parasternal and suprasternal views will be captured with cardiac sector transducers 12S-D and 6S-D. Measurements will be obtained during the examination in accordance with the American Society of Echocardiography's guidelines for a paediatric echocardiogram.[104] All raw data (cine loops and measurements) will be acquired using the EchoPac software (General Electric, Horten, Norway).

Sample size

A Danish cohort study reported a mean neonatal fat mass of 433 g (SD 212 g) in mothers with obesity compared with 331 g (SD 163 g) in mothers with normal weight.[105] Additionally the DALI study found an effect of healthy diet and physical activity counselling compared to standard of care with a difference of -63 gram (95% CI -124 gram to -2 gram, P=0.04).[106] Since we will include women with a BMI of 25 to 44 kg/m², expected to lose 10% of their weight, we do not anticipate achieving an average pre-pregnancy

BMI of 22 kg/m² in the intervention group. As a result, we expect a smaller reduction in neonatal fat mass of 54 grams. To detect this difference between the control and intervention group at a significance level of 5% with a power of 80%, a total of 125 newborns are needed in each group if adjustment for maternal age, BMI and parity as baseline covariates will reduce residual SD in the analysis of covariance (ANCOVA) model to around 140 g. We anticipate that approximately 30% of the randomised women will either not become pregnant or drop out of the trial. Two large Danish cohort studies examining birth rates, including 3,727 and 1,651 women respectively, found that 68% and 70% conceived after 12 cycles. Both studies excluded women with more than six cycles of attempted conception at study entry. They had no exclusion criteria related to BMI or known infertility. To our knowledge, few studies have examined pre-conception lifestyle interventions. Rönö et al. assessing the effect of a pre-conception intervention aimed at preventing GDM found that 67% of women (n=72) in the intervention group and 63% (n=71) in the control group became pregnant.[107] Hence, we will include a total of 360 women in the study, which will establish a birth cohort of valuable size for further follow-up.

To our knowledge, no studies have examined the long-term effects of pre-conception lifestyle interventions on children's health. A review by Amati et al. found an association between infant adiposity and later BMI.[108] Wibaek et al. showed that greater fat mass at birth, measured using PEA POD, was associated to higher cholesterol levels at age 5,[109] Josefson et al. found that both newborn fat mass and birth weight were associated with childhood adiposity.[110] Moore et. al. investigated the relationship between newborn adiposity and childhood obesity, measured using PEA POD. They found neonates with adiposity +1 SD above the mean had a higher BMI, with 23% being overweight or obese by ages 5-6.[15] However, these findings do not allow us to predict the same long-term effects from the 54-gram difference expected in this study, which is a proof-of-concept study to assess whether pre-conception weight loss affects neonatal fat mass.

Sample size calculations were made with SAS Enterprise guide V.7.11.

Randomisation, blinding and treatment allocation

Randomisation will be 1:1. The allocation sequence will be computer-generated simple randomisation with no stratification or balancing enforced, done by an external data science researcher. An investigator at the baseline visit will perform randomisation at the baseline visit using the randomisation module in the software REDCap.[111] The allocation will be concealed by automated assignment using the REDCap randomisation module. In view of the nature of the intervention, this is an open-label study where only the statistician is blinded.

Data collection and data management

Data will be owned by the study consortium and will be stored according to Danish law and applicable guidelines in an encrypted database (REDCap) with access limited to the investigators and support staff. All health-related matters and sensitive personal data will be handled in accordance with the Danish Data Protection Act. Adequate blinding of all personal data during data processing and publication will be ensured. Data will be stored in coded/pseudoanonymised form for 10 years after the last participant has attended the last visit after which it will be transmitted to the Danish Data Archives. All data will be entered directly in REDCap, licensed by the Capital Region of Denmark, or saved electronically. All forms are filled out during (or immediately after) the assessment of a subject. Errors and corrections are logged as provided by the REDCap interface.

Data analysis

The primary analysis will be conducted in the intention-to-treat population including all available data from randomised women and their children regardless of intervention adherence. We target a hypothetical estimand interpreted as the expected effect of the intervention for a woman in the study population, if she becomes pregnant. To achieve this, missing outcomes, including those from women who fail to become pregnant within the 2 years of follow-up, will be handled by multiple imputations, including maternal age, BMI and parity at baseline as predictors in the imputation model together with the primary and secondary outcomes. We will estimate the effect of the intervention using an ANCOVA model that includes maternal age, BMI and parity as baseline predictors. A two-sided p value <0.05 is considered statistically significant.

The secondary analyses will be conducted in the intention-to-treat population with missing data handled similarly to the primary analysis. Continuous scale outcomes will be analysed using an ANCOVA model, including maternal age, BMI and parity as baseline predictors. Binary outcomes will be analysed using risk differences/χ^2 tests (Fisher's exact test in case of low event counts). The p values from the secondary analyses will be adjusted for multiple testing using the method of Benjamini and Hochberg, which controls the false discovery rate. An adjusted p value <0.05 is considered statistically significant.

Adverse events and serious adverse events will be reported in numbers and percentages. Formal statistical comparisons will not be performed due to anticipated lack of power.

The analyses of the primary and secondary outcomes will be repeated in the per-protocol population consisting of participants who remain in the study until childbirth or 2 years postrandomisation without experiencing completed pregnancy and who have completed the intervention with a minimum of 75% participation in

scheduled activities and who have achieved at least 7.5% reduction in weight if assigned to the intervention group.

Descriptive tables will be made to compare the baseline characteristics of the participants who are per protocol with the protocol violators within and between the intervention groups. In case any clinically relevant differences occur between the groups, the analyses will be further adjusted for these as potential confounders.

Subgroup analyses will be performed to evaluate the effect in singleton children born at term.

Additional details and planned sensitivity analyses will be provided in a statistical analysis plan to be submitted for publication before the last participant's last visit and prior to the unblinding of data.

Harms

All women will be asked about adverse events at the clinical visits. All self-reported adverse events will be listed with preferred terms according to the Medical Dictionary for Regulatory Activities, V.3.1.

Patient and public involvement statement

The protocol and intervention have been developed with inputs from focus group discussions and semistructured interviews with Danish women who met the inclusion criteria and expressed a desire to lose weight before pregnancy.[112] In addition, we aim to conduct a longitudinal qualitative study in the PRE-STORK trial. Women will undergo interviews at baseline, at 3 and 6 months, with the aim of identifying barriers and facilitators to adherence.

ETHICS AND DISSEMINATION

Ethical considerations

The study will be conducted in accordance with the ethical principles in the Declaration of Helsinki, with national laws and regulations for clinical research and the regulations for Good Clinical Practice. The study has been registered at the ClinicalTrials.gov. Participants will provide informed consent orally and in writing. All inquiries and examinations involving project participants will be conducted by experienced personnel and in settings that demonstrate great respect and care to avoid stigmatisation.

All participants will undergo comprehensive examinations, facilitating early diagnosis of any concurrent diseases and initiation of timely treatment. Pregnant women will undergo additional ultrasound examinations of the fetus. Furthermore, women and their partners in the lifestyle intervention group will receive care aimed at enhancing their overall health and reducing pregnancy-related complications. All health-related matters and sensitive personal data will be handled in accordance with the Danish 'Act on Processing of Personal Data'.

Equipment used meets the requirement for patient safety. Participation may involve minor inconveniences. Blood collecting can lead to discomfort, and in rare cases a small bleeding or superficial phlebitis. Blood loss will maximally be 700 mL for women, 500 mL for partners, and 9 mL for the children. Complication to the CGM is rare and minimal. A DXA scan involves a low radiation dose of around 0.1 mSv, classified as category 1 by the International Commission on Radiation Protection and the European Commission. There is no discomfort or risks associated with Fibro-Scan, indirect calorimetry, bioimpedance or blood pressure. Qualified personnel will perform fetal ultrasounds, and any concerns regarding the fetus or mother will be addressed following standard procedures. Echocardiography and a standard electrocardiography will be performed by trained personal, are non-invasive procedures and are associated with little or no inconvenience. In case of any congenital heart defects being found, the child will be referred to relevant counselling. The PEA POD examination is non-invasive, without any radiation, and with little or no discomfort for the child. All epigenetic examinations will be based on array techniques not generating findings with impact on the test person. The low-caloric diet is generally considered safe with no significant adverse effects. The exercise programme follows the WHO recommendations. The participants are covered by the Patient Compensation Association according to the Danish Act on the Right to Complain and Receive Compensation within the Health Service.

Overall, the potential benefits and scientific significance are expected to outweigh any potential risks or disadvantages in this clinical trial.

Dissemination plan

All study results (positive, negative and inconclusive) will be presented at international scientific conferences as oral presentations or poster presentations. Furthermore, results will be published in international peer-reviewed scientific journals.

Protocol

The study protocol was approved on 29 September 2022. The present manuscript details the latest version of the protocol (V.2) approved on 9 September 2023. The study protocol has been reported in accordance with the Standard Protocol Items: Recommendations for Clinical Interventional Trials guidelines (additional file 1).

Study status

Collection of data will take a total of 5 years, starting with the first participant's first visit in October 2022 and the last participant's last visit at the end of 2027. Data analyses, publications and presentations at conferences will be initiated in 2024 and forward.

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Contributors SST, LGG and TV conceptualised the study. All authors contributed to the study design, methodology, assessments and/or planning of the intervention. KB and JLF were involved in developing the data analysis plan and conducting statistical analysis. NK, JHD, LK, SF, TB, ND, EG and LL conducted investigations. NK, MYJ, SST, LGG and TV drafted the original manuscript. NK, RES and MYJ were responsible for project administration. All authors have contributed to and approved the final version of the manuscript. Authorship eligibility adheres to the Vancouver guidelines. TV is the guarantor of this work.

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Competing interests NK, JHD, RES, MLP, SF, NG, EG, LL, KKN, AA, LGG and TV are employed at Steno Diabetes Center Copenhagen, a public hospital and research institution under the Capital Region of Denmark, which is partly funded by a grant from Novo Nordisk Foundation. RES owns shares in Novo Nordisk A/S. MYJ is currently employed in Novo Nordisk A/S. FKK has served on scientific advisory panels, been part of speaker's bureaus for, served as a consultant to and/or received research support from 89bio, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Gubra, Novo Nordisk, Sanofi, Structure Therapeutics, Zealand Pharma, Zucara; is a co-founder and minority shareholder in Antag Therapeutics and owns shares in Eli Lilly, Novo Nordisk and Zealand Pharma; is currently employed by Novo Nordisk. TB has received lecture fees from Novo Nordisk. LK owns shares in Novo Nordisk A/S. SF has been part of speaker's bureaus for Novo Nordisk. RB has received research grants from the Novo Nordisk Foundation. AA has received lecture fees from Eli Lilly. SST has received grants, honoraria for lectures and membership on an advisory panel for Novo Nordisk, Research grant from Embla, Horaria for lectures from Merck and Ferring. LGG owns shares in Novo Nordisk A/S. TV has served on scientific advisory panels, been part of speaker's bureaus for, served as a consultant to and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GSK, Novo Nordisk, Sanofi and Sun Pharmaceuticals.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

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