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Protocol for the FitMum study: Effects of structured supervised exercise training and motivational counselling during pregnancy on physical activity level and health of mother and offspring

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Abstract

- **Introduction**: A physically active lifestyle during pregnancy improves maternal and offspring health, but can be difficult to follow. In Denmark, less than 40% of pregnant women meet the physical activity (PA) recommendations. The FitMum study aims to explore strategies to increase PA during pregnancy among women with low PA. It will evaluate the efficacy of two separate exercise regimens.
- **Objective**: To present the FitMum protocol, which evaluates the effects of structured supervised exercise training and motivational counselling supported by health technology on PA level during pregnancy.
- **Methods**: A single-site three-arm randomized controlled trial, which aims to recruit 220 healthy, pregnant women with gestational age (GA) no later than week 15 and whose PA level does not exceed one hour/week. Participants are randomized to either structured supervised exercise training consisting of three weekly exercise sessions, motivational counselling supported by health technology, or a control group receiving standard care. The interventions take place from randomization until delivery.
- **Primary outcome**: Min/week of moderate-to-vigorous-intensity PA as determined by a commercial activity tracker, collected from randomization until GA of 28 weeks and 6 days.
- **Secondary outcome:** Gestational weight gain.
- **Additional outcomes**: Complementary measures of PA; clinical and psychological health parameters in participant, partner, and offspring; analyses of blood, placenta and breast milk samples; process evaluation of interventions; personal understandings of PA.
- **Conclusion**: The study will provide valuable guidance and scientific evidence about the efficacy and applicability of two different PA regimens during pregnancy and will provide novel insight into the potential health benefits for the mother and for the offspring.
- **Strengths and limitations of this study:**
- The efficacy of structured supervised exercise training and motivational counselling supported by health technology to improve physical activity and weight gain of pregnant women is compared in a randomized controlled trial.
- The trial involves complex interventions and is held in one site only, so generalizability and fidelity might be a concern. Yet, as one of the additional outcomes, a process evaluation is conducted alongside the trial to explore how the interventions are carried out and adapted.
- The study is comprehensive and multidisciplinary in its design. Many different methodologies are used and both mother, partner and offspring are studied.
- Activity trackers can increase physical activity level and are feasible tools in everyday life, but commercial activity trackers have limited validity for quantification of physical activity.

- Physical activity is extensively measured using three different methods: commercial activity trackers, gold standard doubly labelled water, and the validated Pregnancy Physical Activity Questionnaire.

Trial registration: ClinicalTrials.gov (# NCT03679130). Registered September 20, 2018.

Protocol version: This paper was written per the study protocol version 8 dated August 28, 2019.

Introduction

Although the health effects of physical activity (PA) are widely acknowledged, the means of how to implement and maintain PA in everyday life are lacking (1). Pregnancy can be regarded as a window of opportunity to implement good habits of PA as pregnant women are in regular contact with health professionals and likely motivated to adopt healthy behaviours, as illustrated by reduced alcohol consumption and smoking cessation (2–4). On the other hand, pregnancy can be conceived as an opportunity to be exempt from demands about fitness and bodily ideals, or be experienced as a problematic and troublesome time with fatigue and discomfort (5,6). Moreover, pregnancy is a short period when it comes to change of habits (6), and that may affect the motivations and challenges to be physically active. Furthermore, differences in work status, social relations, the family situation, as well as material and structural conditions may contribute to the implementation of PA (7).

Insufficient PA during pregnancy is a global problem (8–12). It is a significant public health issue, as increasing evidence suggests that lifestyle during pregnancy influences health in the mother and her offspring (4,13). Regular PA during pregnancy promotes clinical and metabolic health in mother and offspring and reduces the number of complications during pregnancy and delivery (14–19). PA reduces gestational weight gain (20–26), the risk of gestational diabetes mellitus (27–32), the intensity of low back pain (33), the risk of caesarean delivery (22,29,34–37) and improves maternal body composition (38). Also, a physically active pregnancy improves the health of the offspring by normalizing birth weight (22), reducing the risk of preterm delivery (39,40), improving neonatal body composition (41,42), as well as placental function (43,44), resulting in optimized intrauterine growth conditions.

The Danish Health Authorities recommend that healthy pregnant women are physically active for at least 30 min/day at moderate intensity (45), but only 38% of Danish pregnant women achieve the recommended level (46). Several barriers to PA during pregnancy are addressed in the literature (47), including anxiety about over-doing exercise, low motivation to adopt an active lifestyle during pregnancy, changing energy levels throughout the pregnancy, and lack of time to be physically active (48). The latest recommendations on lifestyle interventions during pregnancy support individualized advice about how to increase the PA level rather than a generic approach (6), as pregnant women prefer personalized information (49). Consequently, policymakers, healthcare professionals, and pregnant women urge for evidence-based guidance on how to implement PA in everyday life during pregnancy safely and effectively, and with approaches that meet the needs, preferences, and choices of the pregnant woman.

During the past decades, many PA intervention studies in pregnant women have been conducted on overweight and obese populations (23,24,26,28,50–57) as well as in healthy normal-weight pregnant women (20,21,32,33,58–61). Still, none of these has focused primarily on investigating the effect of the exercise interventions on actual PA level in pregnant women nor used novel objective methods to measure actual PA levels. Structured supervised exercise training or motivational counselling have been applied separately in pregnant women (20,21,23,24,26,28,32,33,50–55,58–63), but the relative

efficacy has not been compared, which hampers the evidence-based implementation of effective exercise programs into everyday life.

Objective

This paper describes the protocol for the FitMum study, which is centred around a randomized controlled trial (RCT). The FitMum RCT aims to evaluate the effects of structured supervised exercise training (EXE) and motivational counselling supported by health technology (MOT) compared to standard care (CON) on PA level and body weight gain during pregnancy. Additional aims are to investigate the effects of EXE and MOT on clinical and metabolic health parameters in mother and offspring. We will also explore how the FitMum exercise programs are carried out and adopted by conducting a process evaluation. In addition, we explore the personal attribution of meaning to the experiences and practices of PA among the participants. Furthermore, we investigate how social, structural, and cultural factors facilitate or hinder the successful implementation of exercise during pregnancy.

Methods

Study design

The FitMum RCT is a single-site, three-arm trial.

Setting

The study is carried out at the Department of Gynaecology and Obstetrics, Nordsjaellands Hospital (NOH), Hillerod, in the Capital Region of Denmark. NOH is a public hospital and participation in FitMum is free of charge.

Participants

220 healthy, pregnant women will be included. Inclusion criteria are an obtained written informed consent, maternal age of 18 years or older, gestational age (GA) of max. 15 weeks, ultrasonic confirmed viable intrauterine pregnancy, body mass index of 18.5-45 kg/m^2 and body weight <150 kg (pre-pregnancy weight or first measured weight in pregnancy), ability to wear a wrist-worn activity tracker 24/7 until one year postpartum and having a smartphone. Exclusion criteria are structured exercise at moderate-to-vigorous intensity for more than one hour/week during early pregnancy, previous preterm delivery, obstetric or medical complications, multiple pregnancies, non-Danish speaking, or alcohol or drug abuse.

Recruitment and inclusion

Participants are recruited 1) *via* booking confirmation of a first-trimester scan, 2) at face-to-face meetings during the first-trimester scan, and 3) through posters, flyers, and social media. Before inclusion, interested women answer an online one-page pre-screening questionnaire. Eligible participants and their partners are invited to the first visit at NOH as soon as possible and not later than GA of 14 weeks and 6 days. At visit 1, the woman is verbally informed about the study and screened according to in- and exclusion criteria. Women who have not had a first-trimester scan are vaginally scanned to confirm a singleton, viable intrauterine pregnancy. All eligible women are included and

written informed consent obtained. Written informed consent is also obtained from the biological father or other holders of custody as biological samples are collected from the offspring and, if known, from the biological father. A short semi-structured interview with the participant is recorded. The interview provides knowledge of the participant's thoughts on participating in a research project, knowledge of prior and current PA level as well as experiences with health technologies. After inclusion, anthropometric and demographic information and a blood sample are collected.

At the end of visit 1, the participant receives a commercial activity tracker, Garmin Vivosport. The participant is instructed to wear the tracker continuously 24/7 from the one-week baseline period until one year postpartum, except during charging. The activity tracker is water-resistant and determines the frequency, duration, and intensity of activity periods on a minute-to-minute basis. The data from the activity tracker are wirelessly synced to the associated app, Garmin Connect, provided by Garmin International, and the research platform Fitabase (Small Steps Labs LLC), through which the compliance of wearing and synchronizing the data from the tracker are continuously monitored during the study.

Baseline period and randomization

After inclusion, the baseline PA level of the participant is measured by the activity tracker for one week. After the baseline period, participants are randomized into the CON, EXE, or MOT groups (Figure 1). The target number of participants randomized to each group is 44, 88, and 88, respectively, to have more participants in the intervention groups. Randomization is performed via a numbered randomization list administered through the database Research Electronic Data Capture (REDCap), and the investigators are blinded to the procedure. Blinding of participants is considered impossible due to the inherent content of the exercise interventions. The participant is informed about the assigned group by email, and participants in EXE and MOT receive written information containing guidelines from the Danish Health Authorities about PA during pregnancy.

Patient and public involvement

Template for Intervention Description and Replication (64) was used as inspiration for the development and description of the study. As a part of the development phase, stakeholders in the field were involved in discussions and sharing of knowledge. Additionally, 27 semi-structured interviews with Danish pregnant women, midwives, and obstetricians were performed to explore the feasibility of such study as well as the motivational factors and barriers to PA during pregnancy. Participants are not directly involved in recruitment and conduct of the study, but at process evaluation is carried out and personal understandings of the participants are obtained via interviews (see below). The insights from the study will be shared with the participants at an information meeting after the end of the study.

Interventions

Standard care at the hospital

All three groups are offered the standard care that applies to women giving birth at NOH. It consists of three appointments with their general practitioner (GA weeks 6-10, 25 and 32), five to six midwife

consultations (GA weeks 14-17, 29, 36, 38, 40 and if still pregnant around week 41 as well) and ultrasonic scans at GA weeks 12 and 20.

Standard care control group (CON)

Participants in CON wear an activity tracker to determine the activity level. The face of the tracker looks like a normal watch showing only time and battery life.

Structured supervised exercise training intervention (EXE)

The targeted PA level for all participants in EXE and MOT is at least 30 min/day at a moderate intensity as recommended to healthy pregnant women (6). In EXE, exercise training is in teams and supervised by health professionals (exercise physiologists, physiotherapists, public health scientists). It consists of three weekly one-hour exercise sessions at moderate intensity, including two exercise sessions in a gym and one in a swimming pool. The gym sessions consist of a combination of aerobic and resistance training with 30 min stationary bike training (a combination of hill climbing and high cadence intervals) and 30 min of e.g. elastic bands, exercise balls, mats, dumbbells or own body weight. In the swimming pool, participants do 15 min of swimming and 45 min of water exercises with plates, balls, dumbbells or own body weight. Moderate intensity during training sessions is assessed using both heart rate monitoring of 65-80% of age-predicted maximal heart rate (from the activity tracker) and perceived exertion in the range of 12-14 on Borg's conventional 6-20-point scale (65), as recommended by the American College of Obstetricians and Gynaecologists (14). If a participant experiences any pain or needs to slow down, the content of exercise sessions is adjusted individually accordingly. Exercise sessions are offered at seven different times per week, and participants are recommended to sign up for three of these sessions. The sessions are held early mornings or late afternoons all weekdays, and before noon on Fridays and Saturdays.

Motivational counselling supported by health technology (MOT)

This intervention comprises four individual and three group counselling sessions as well as weekly SMS-reminders. The overall focus of both the individual and group counselling sessions is built based on what already motivates the participants to increase or maintain their PA level. The motivation technique applied is inspired by motivational interviewing (66), self-determination theory (67), and behaviour change techniques (68).

All four *individual sessions* last one hour and are led by professional health counsellors (exercise physiologists, physiotherapists, public health scientists). The sessions aim to discuss the participant's barriers, wishes, needs, knowledge, and former PA experiences to identify individual characteristics and motivation towards a more physically active lifestyle. Aside from measuring the PA level, the activity trackers are also used as an intervention element to motivate the participants to increase their PA levels (69). During the individual sessions, feedback on recent PA performances is provided based on activity data acquired from the activity tracker, to give the participants insight into their PA level. The participants will, with guidance from the counsellor, set their own activity goals and make an

individual action plan to increase the PA level, which may have a motivating effect on PA behaviour (69,70). Individual sessions are scheduled during the daytime but as appropriate for the participant as possible.

The first *group session* lasts one hour and aims to inform the participants about guidelines for PA, benefits associated with PA during pregnancy, and possible ways to increase PA during pregnancy. In the following two two-hour group sessions, the interaction between the participants is used to create meaningful group processes such as support, experience exchange, reflection, learning, and development. These sessions focus on discussion of relevant topics concerning PA during pregnancy, and the counsellor acts as a facilitator through the session, with the topics of conversation chosen by the participants. Issues like postpartum PA, the pelvic floor, uterine contractions, diastasis recti, and myths about pregnancy PA are discussed. Group sessions are held late afternoons, or before noon for those being on maternity leave.

The weekly SMS-reminders have supportive and motivating content and are used to encourage the participants to achieve a moderate PA level. The texts are chosen based on every participant's PA level during the last week measured by the activity tracker. One example of the text: "You have been exercising regularly for an extended period of time. Well done. Good habits make it easier for you to continue as your belly gets bigger and heavier."

Outcome measures

The data collection procedures are illustrated in Table 1.

Primary outcome: physical activity level

The primary outcome of FitMum RCT is min/week of moderate-to-vigorous-intensity PA measured continuously from randomization to GA of 28 weeks and 6 days as determined by a wrist-worn activity tracker, Garmin Vivosport, with built-in heart rate monitor and accelerometer.

Secondary outcome: gestational weight gain

Body weight of the participant before pregnancy is self-reported. Body weight during pregnancy is measured five times from inclusion until delivery on the same scale (Seca 799) with the participant in light clothes and without shoes.

Additional outcomes

Complementary measures of physical activity

Complementary measures of PA are obtained by the Danish version of 'Pregnancy Physical Activity Questionnaire' (PPAQ) (71) named PPAQ-DK, and by the doubly labelled water technique (72). PPAQ is a semi-quantitative and subjective instrument, which has been validated (71) and is considered one of the most valid and reliable questionnaires for assessment of PA level in pregnant women (73). Our research group has translated PPAQ into Danish and validated it in a Danish pregnant population (manuscript in review).

The doubly labelled water technique is the 'gold standard' technique to measure free-living energy expenditure objectively, and is safe, even for pregnant women, as it relies on stable, non-radioactive isotopes (74–77). The participant is administered a glass of water for oral intake containing 0.1 g of 99.98 % $^{2}H_2O$ and 1.6 g of 10% ^{18}O per kg body weight. In total, five post-dose urine samples are collected in the morning (not the first urine void of the day); on the day after oral water dosage, and after four, seven, 11, and 14 days. The urine samples are stored in the participant's freezer and later at -80 °C.

In addition, PA of the participant is determined from GA week 29 until delivery and in the first year postpartum by the activity tracker. The measures of PA include active calories, active time, steps, heart rate, moderate- and vigorous-intensity activity, floors climbed, MET-min/week, and type of activity, which is recognized automatically by the tracker.

Clinical and psychological health parameters in participant, partner, and offspring

A variety of clinical and psychological health parameters are obtained from the participant, her partner, and her offspring. *Clinical data* regarding pregnancy, delivery, and neonatal outcomes are collected from medical records. *Health-related quality of life* is determined in the participant by the Danish version of the Medical Outcomes Study Short Form 36 (SF-36) (78,79), which has also been validated in pregnancy (80). *Exercise self-efficacy* is determined by the Danish version of the Pregnancy Exercise Self-Efficacy Scale (P-ESES) (81). P-ESES has been translated into Danish and validated in a Danish pregnant population by our research group (82). *PA motivation* is determined by the Danish version of the Behavioural Regulation in Exercise Questionnaire (BREQ-2) (83–85), which is the most widely used measure of the continuum of behavioural regulation in exercise psychology research. *Sleep quantity and quality* are assessed in the participant by the activity tracker and by the Danish version of the self-administered questionnaire Pittsburgh Sleep Quality Index (PSQI) (86,87). The PSQI is considered a valid and reliable tool to assess sleep metrics among pregnant women (88). In addition, a validation of activity trackers to measure sleep will be conducted using polysomnography in a sub-group of women already participating in the FitMum study. *Sick leave and pelvic and low back pain* are registered by asking the participant whether she has been absent from work/study and on sick leave during her pregnancy and whether she has experienced pelvic and low back pain before and during her pregnancy. *Maternal body composition* is determined from total body water measured by doubly labelled water technique and by a postpartum Dual-energy X-ray absorptiometry (DXA) scan. *Offspring growth:* Head circumference, length, and weight is measured at birth and at general practitioners at five weeks, five months, and 12 months postpartum. Participants receive an electronic questionnaire and fill out the anthropometric data along with information on offspring dietary habits and vaccine-status. *Parental mental wellbeing* is assessed 6-8 weeks after birth. Both parents or holders of custody receive a questionnaire consisting of the Edinburgh Postnatal Depression Score, and Gotland Depression Scale that combined is a screening tool for postnatal depression (89–92) used in the Danish postnatal care. *Psychomotor development of the offspring* is assessed by the validated Ages and Stages Questionnaire 3 (ASQ-3), which is administered electronically to participants 12 months

after the due date. ASQ-3 pinpoints developmental progress in the fields of communication, gross motor, fine motor, problem-solving, and personal-social skills. The administration of ASQ-3 relative to due and not to birth date aims to correct for variance in cognitive and motor skills due to premature birth. *Offspring physical activity* is assessed for seven days by an infant activity tracker (Actigraph GT3X+) 12 months after the due date. The tracker detects level, intensity, and pattern of physical activity.

Analyses of blood, placenta and breast milk samples

Plasma metabolites and hormones are assessed in maternal and paternal venous blood. The blood samples will be analysed for concentrations of glucose, cholesterol (total, high and low density), triglyceride, insulin, free fatty acids, amino acids, interleukin-6, and C-reactive protein. Venous blood is obtained from the umbilical cord within 30 min after delivery of the placenta. The blood will be analysed for concentrations of glucose, cholesterol (total, high and low density), triglyceride, insulin, c-peptide, free fatty acids, amino acids, adiponectin, and leptin. Furthermore, epigenetic profiling at the level of *DNA methylation* will be performed in maternal, paternal, and umbilical cord blood mononuclear cells. Bioinformatic comparison of DNA methylomes from parents and offspring will infer on the DNA methylation marks that are modulated by maternal exercise and transmitted to the offspring. Information on DNA methylomes from each parent will allow us to distinguish between maternally and paternally transmitted epigenetic profiles to the offspring. Principal component analyses will be used to identify the specific metabolic or anthropometric features of the mother that are associated with a specific DNA methylation footprint transmitted to the offspring. *Placental function* is assessed from samples taken within 30 min after delivery of the placenta. The samples are immediately frozen on dry ice and stored at -80 °C. Analyses will include RNA-seq, non-targeted metabolomics, RT-qPCR, Western blot, histology, and immunohistochemistry. *Breast milk* is obtained from a single feed at the day of visit 5 and stored at -80 °C for later metabolomic and lipidomic analyses.

Process evaluation of interventions

A process evaluation is made using quantitative and qualitative methods to provide insight into mechanisms through which interventions bring about change, assess fidelity and quality of implementation, clarify causal mechanisms, and identify contextual factors associated with variations in outcomes (93–95). Integrating process evaluations alongside outcome data are recommended by the UK Medical Research Council guidelines to develop and evaluate complex interventions to improve the interpretation of the outcomes, design more effective interventions, and apply them appropriately across groups and settings by understanding the implementation and functioning of interventions in a given context (94,96). The RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework is used to improve reporting on key issues related to the implementation and external validity of FitMum RCT (97).

Personal understandings of physical activity

The qualitative dataset is comprised of 220 short standardised screening interviews, 30 semi-structured interviews, 70 observations, five sets of auto-ethnographies, visual material, as well as drop-out and follow-up interviews. This sub-project will explore the physical and mental health and wellbeing of the participants, their social relations, PA levels, and their experience of pregnancy to identify the challenges and barriers of PA during pregnancy. Personal understandings of PA in the everyday life of the participants are determined at inclusion, GA week 34, and one year postpartum, in approximately ten participants from each of the three study groups.

Changes during the COVID-19 pandemic

During the COVID-19 pandemic (in Denmark from March 11th 2020), all interventions and visits (except the birth) are converted into online versions using Zoom Cloud Meetings or telephone. In EXE, the swimming pool sessions are cancelled, and all sessions are land exercise sessions consisting of 30 min of aerobic exercise where the participants exercise on their own (e.g. biking, power-walking, dancing, aerobics) followed by 30 min of supervised online group resistance training. All individual and group MOT sessions are held online.

As much data as possible is collected during the pandemic, but some clinical data have not been possible to obtain due to limitations on non-urgent visits to the hospital. No blood samples are obtained at the virtual 'visits', the women are weighed at home, and symphysis-fundal height measurements are not obtained. No doubly labelled water is administered at the virtual 'visit' 2. The women's body weight at visit 4 is noted by the midwives on the day of giving birth, but biological samples are not collected. No DXA-scans or breast milk samples are collected at 'visit' 5.

Data management and analysis

Data management

The activity tracker data are collected by Fitabase that regularly backs up the data. A participant who does not synchronize the tracker for seven days or more is reminded by email, text message, or phone call. All tracker data are exported from Fitabase to R (98) for data analysis. Tracker data are utilized to calculate the non-wear time; a week is included in the analysis if the week has four or more days with complete data. A day that has six hours or more of non-wear time is excluded and considered a missing day. An electronic case report form (e-CRF) is utilized to collect all clinical data related to the trial. Data are stored in coded form according to the rules of the Danish Data Protection Agency. Personal data processing is complied with, concerning the Act on Processing of Personal Data. The e-CRF is completed by the investigators at the time of the participant's visits at NOH so that it always reflects the latest observations for the participant. Data will be stored for 25 years, after which they will be transferred to the Danish National Archives "Rigsarkivet" in an anonymized format.

Sample size

FitMum RCT has been powered to detect an overall significant difference in the primary outcome between the three groups as well as a significant difference between the two intervention groups (EXE

vs. MOT) with average activity levels of 60 (CON), 210 (EXE) and 150 (MOT) min/week. The standard deviation was set at 116 min/week and based on the results from Oostdam et al. (51). The required sample size is determined to obtain a power of 80% with a family-wise significance level of 5%. The sample size calculation showed that the required number of participants is 35 in CON and 70 in each of the two intervention groups due to the randomization ratio of 1:2:2 to CON, EXE, and MOT, respectively. Based on an expected lost-to-follow-up rate of 20%, as seen in similar exercise studies in pregnant women (28,32,33,51), we plan to include 44 participants in CON and 88 participants in each of the two intervention groups, making a total of 220 participants.

Statistical methods

Data analyses of both primary and secondary outcomes will be performed using intention-to-treat analyses. In addition, a dose-response model will be estimated to quantify the relationship between adherence to the intervention (proportion of attendances in the planned EXE and MOT sessions, respectively) and the activity level. Moreover, analyses describing associations between the level of physical activity, as measured by the activity tracker, and the secondary and additional outcomes will be performed. Baseline data will be reported as averages and standard deviations (medians and interquartile ranges) or frequencies and proportions as appropriate. No interim analyses will be performed on the primary and secondary outcomes. The analysis of the primary outcome will be performed using a linear model with the randomization group as a categorical covariate and with adjustment for baseline PA level. Hypothesis tests will be performed using likelihood ratio tests. Statistical analysis will be carried out using R (98). Analyses of the primary outcome will be performed by a statistician blinded from the intervention allocations. Investigators will perform analyses of baseline data and secondary and additional outcomes under the supervision of a statistician.

Trial status and dissemination

The recruitment of participants started in September 2018. Data collection of the primary outcome is expected to complete early 2021. Full data collection is expected to be complete in 2022.

The FitMum study will provide evidence-based knowledge that can contribute to improving national and international recommendations of PA during pregnancy and to new, effective, and simple guidance to implement health technology-supported exercise programs to pregnant women. Based on the results and the process evaluation, the knowledge and tools from the FitMum study can be transformed into initiatives in municipalities and hospitals to improve the health and quality of life for both mother and child, and for preventing the development of lifestyle-related diseases across generations.

Findings will be submitted for publication in peer-reviewed scientific journals and disseminated at national and international conferences. Further, results will be disseminated to the general public in relevant media and to health professionals via science theatre performances.

Ethical aspects

The FitMum study adheres to the principles of the Helsinki declaration. The study is approved by the

Danish National Committee on Health Research Ethics (# H-18011067) and the Danish Data Protection Agency (# VD-2018-336).

All participants consent in written form before inclusion and are informed that participation in the FitMum study is voluntary. Participants are informed that they may withdraw from the study at any time, and that withdrawal of consent will not affect any subsequent pregnancy and delivery process at NOH. The participant has time to ask questions and is allowed 24 hours to deliberate on study participation before the obtainment of written informed consent.

FitMum RCT is designed based on recommendations of appropriate PA during pregnancy (14,45,99,100), and although there are anatomic and physiological changes during pregnancy, PA during an uncomplicated pregnancy is safe (14,22,29,40,60,101–104). All information about adverse events and serious adverse events are documented consecutively and will be reported. A participant with a serious obstetric or medical complication will be discontinued from interventions.

Discussion

The FitMum study aims to evaluate the effects of structured supervised exercise training and motivational counselling supported by health technology on PA level during pregnancy to generate evidence about *how* to implement PA in healthy pregnant women's everyday life. Previous studies have investigated the effect of different lifestyle interventions in normal weight (23,24,26,28,50–57), overweight, and obese pregnant women (20,21,32,33,58–61) on various health outcomes. However, neither has focused primarily on investigating the effect of PA interventions on actual PA level determined by novel objective methods. In addition, the FitMum study compares the effect of two different PA interventions to explore strategies to implement PA programs into pregnant women's everyday life. Moreover, offspring of FitMum participants is studied for one year after birth whereby knowledge on the effect PA during pregnancy on offspring health is obtained.

Consumer-based wearable activity trackers tend to increase the PA level when they are used as an intervention tool or as part of an intervention (105). Activity trackers are often relatively light in weight, comfortable to wear, and rechargeable (106). In addition, using an activity tracker to measure PA during pregnancy is recommended (107), and it is feasible and has a reasonable compliance rate during pregnancy and after giving birth (108). However, there are some challenges and limitations of using activity trackers in a long intervention study. Firstly, the participants must recharge the device and synchronize their data approximately once weekly, which puts a burden on the participants and challenge the adherence and compliance. Secondly, we cannot control the interaction of CON participants with the tracker. Thirdly, the main goal for the tracker's design is a comfortable wear, yet long-time wearing may cause skin irritation and discomfort (109). Moreover, the unavailability of raw data and algorithms used by the manufacturer creates a limitation in the validation of PA metrics (106). Therefore, measuring PA by a variety of methods, and performing a comparison with a gold standard method, the doubly labelled water technique, will be conducted to obtain comprehensive measures of PA behaviours in FitMum participants.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Authors' contribution

BS initiated the FitMum study together with LT and is the principal investigator of FitMum RCT. EL is the clinical trial manager. CBR, SdPK and BS led the protocol development with contribution from SA, ADA, JB, TDC, SM, AKJ, GT, APJ, JEL, GvH, EA, RB, OHM, HTM, LT, and EL. CBR, SdPK, SA, ADA, JB, TDC, SM, EL and BS constitute the clinical core group that guides the practical performance of FitMum RCT. CBR, SdPK and ADA are conducting intervention activities together with research assistants and master students. CBR, SdPK, SA and ADA will perform most of the data analysis along with AKJ. Analyses of the primary outcome will be performed by AKJ. All authors read, contributed to and approved the final version of the manuscript.

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Table 1: Procedures and measurements in the FitMum study

Visit number Gestational age (week+days)	Visit 1 Screening and baseline testing Max. 15+0	E-mail Randomization One week after inclusion	Visit 2 Week 28+0-6	Visit 3 Week 34+0-6	Visit 4 Delivery Approximately week 40	Visit 5 7-14 days after delivery	 One year after delivery
Ultrasound scan	x						
Verbal information about study	x						
Medical interview to assess in- and exclusion criteria	x						
Demographic and anthropometric data	x						
Medical history, concomitant disease, and previous medication	x						
Medical history, PA level, demographic and anthropometric data of the participant's partner	x						
Written informed consent	x						
Activity tracker and associated oral and written information	x						
Randomization		x					
METHODOLOGY FOR OBTAINING ENDPOINTS							
Activity tracker	Continuously during the trial and one year after delivery						
Maternal body weight	x		x	x	x	x	Six times at home during postpartum

Doubly labelled water			x				
Questionnaires: PPAQ-DK, SF-36, PSQI, P-ESES, BREQ-2, sickness absence + pelvic and low back pain	x		x	x			x
Maternal blood samples	x		x	x	x		
Paternal blood sample					x		
Umbilical cord blood sample					x		
Placenta samples					x		
DXA-scan						x	
Breast milk sample						x	
Qualitative interview	x			x			x
Observation and autodocumentation		Recurring					
ASQ-3							x
Growth assessment at general practitioner							5 weeks, and 5 and 12 months
Parental mental well-being questionnaire							6-8 weeks postpartum
Seven-day child accelerometer							x
SAFETY							
Record adverse events			x	x			
Symphysis-fundal height			x	x			

ASQ-3: Ages and Stages Questionnaire 3, BREQ-2: Behavioural Regulations Exercise Questionnaire, DXA: Dual-energy X-ray absorptiometry, P-ESES: Pregnancy Exercise Self-efficacy Scale, PPAQ-DK: Pregnancy PA Questionnaire (Danish version), PSQI: Pittsburgh Sleep Quality Index, SF-36: The Medical Outcomes Study Short Form 36.

Figure legends

Figure 1: Flow diagram of the FitMum randomized controlled trial

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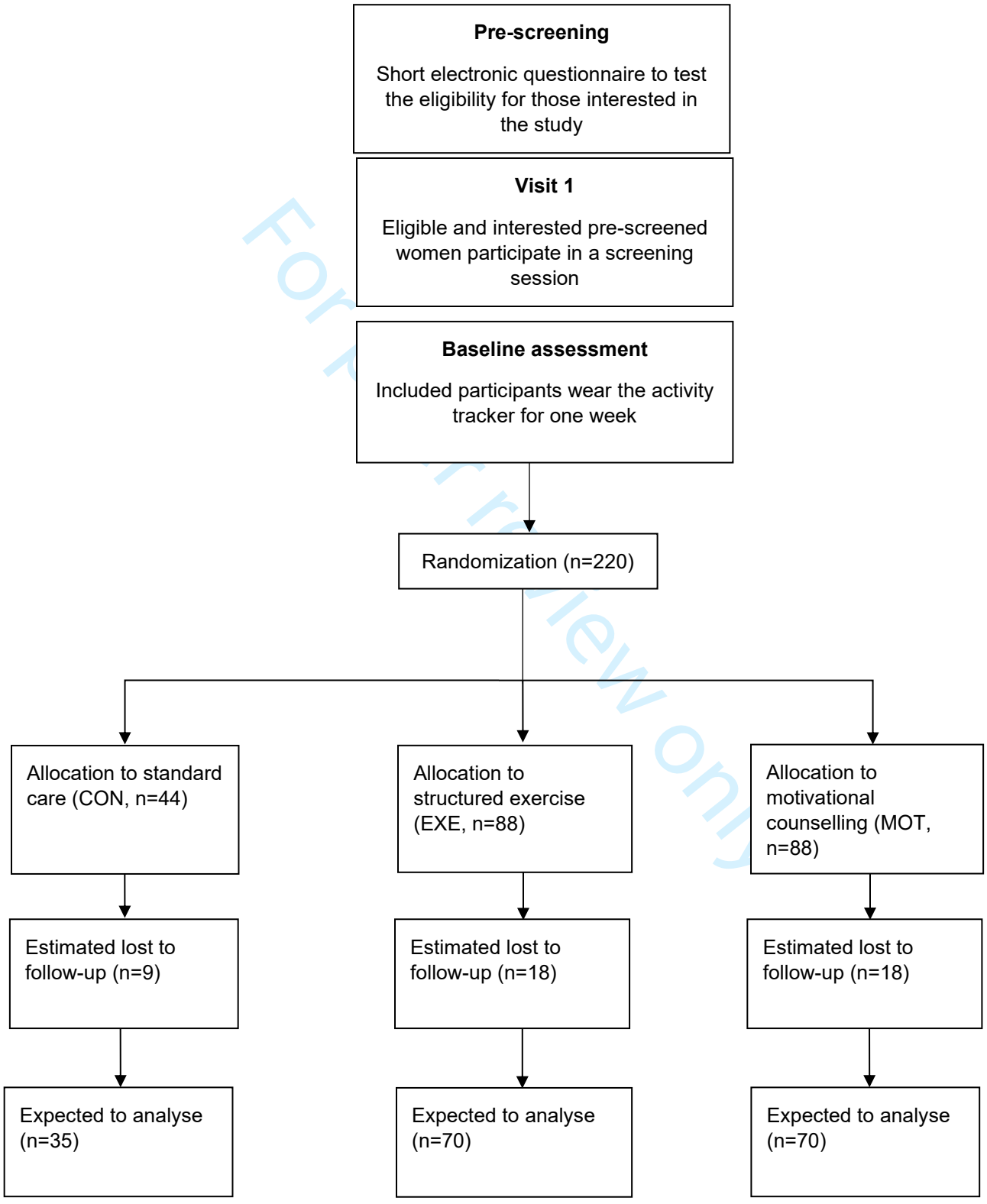

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Structured supervised exercise training or motivational counselling during pregnancy on physical activity level and health of mother and offspring: FitMum Study Protocol

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Structured supervised exercise training or motivational counselling during pregnancy on physical activity level and health of mother and offspring: FitMum Study Protocol

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Abstract

- **Introduction**: A physically active lifestyle during pregnancy improves maternal and offspring health, but can be difficult to follow. In Denmark, less than 40% of pregnant women meet physical activity (PA) recommendations. The FitMum study aims to explore strategies to increase PA during pregnancy among women with low PA and assess the health effects of PA. This paper presents the FitMum protocol, which evaluates the effects of structured supervised exercise training or motivational counselling supported by health technology during pregnancy on PA level and health of mother and offspring.

- **Methods and analysis**: A single-site three-arm randomized controlled trial, which aims to recruit 220 healthy, pregnant women with gestational age (GA) no later than week 15 and whose PA level does not exceed one hour/week. Participants are randomized to one of three groups: structured supervised exercise training consisting of three weekly exercise sessions, motivational counselling supported by health technology, or a control group receiving standard care. The interventions take place from randomization until delivery. The primary outcome is min/week of moderate-to-vigorous-intensity PA as determined by a commercial activity tracker, collected from randomization until GA of 28 weeks and 6 days, and the secondary outcome is gestational weight gain. Additional outcomes are complementary measures of PA; clinical and psychological health parameters in participant, partner, and offspring; analyses of blood, placenta and breast milk samples; process evaluation of interventions; personal understandings of PA.

- **Ethics and dissemination:** The study is approved by the Danish National Committee on Health Research Ethics (# H-18011067) and the Danish Data Protection Agency (# VD-2018-336). Findings will be disseminated via peer-reviewed publications, at conferences, and to health professionals via science theatre performances.

- **Strengths and limitations:**
  - The efficacy of structured supervised exercise training and motivational counselling supported by health technology to improve physical activity and reduce weight gain of pregnant women is directly compared in a randomized controlled trial.
  - The trial involves complex interventions and is held in one site only, so generalizability and fidelity might be a concern. Yet, as one of the additional outcomes, a process evaluation is conducted alongside the trial to explore how the interventions are carried out and adapted.
  - The study is comprehensive and multidisciplinary in its design. Many different methodologies are used, and mother, partner and offspring are studied.
  - Activity trackers can increase physical activity level and are feasible tools in everyday life, but commercial activity trackers have limited validity for the quantification of physical activity.

- Physical activity is extensively measured using three different methods: commercial activity trackers, gold standard doubly labelled water, and the validated Pregnancy Physical Activity Questionnaire.

Trial registration: ClinicalTrials.gov (# NCT03679130). Registered September 20, 2018.

Protocol version: This paper was written per the study protocol version 8 dated August 28, 2019.

Introduction

Although the health effects of physical activity (PA) are widely acknowledged, the means of how to best implement and maintain PA in everyday life are lacking (1). Pregnancy can be regarded as a window of opportunity to implement good habits of PA as pregnant women are in regular contact with health professionals and are likely motivated to adopt healthy behaviours, as illustrated by reduced alcohol consumption and smoking cessation (2–4). On the other hand, pregnancy can be seen as an opportunity to be exempt from fitness demands and bodily ideals, and can be experienced as a troublesome time due to fatigue and discomfort (5,6). Moreover, pregnancy is a relatively short period of time in regards to forming new habits (6), and that may affect the motivations and challenges in being physically active. Furthermore, differences in work status, social relations, and family situations, as well as varying material and structural conditions, may contribute to the implementation of PA (7).

Insufficient PA is a global problem (8) that occurs also during pregnancy (8–12). It is a significant public health issue, as increasing evidence suggests that lifestyle during pregnancy influences health in the mother and her offspring (4,13). Regular PA during pregnancy promotes clinical and metabolic health in both mother and offspring and reduces the number of complications during pregnancy and delivery (14–19). PA reduces gestational weight gain (20–26), the risk of gestational diabetes mellitus (27–32), the intensity of low back pain (33), the risk of caesarean delivery (22,29,34–37) and improves maternal body composition (38). Additionally, a physically active pregnancy improves the health of the offspring by normalizing birth weight (22), reducing the risk of preterm delivery (39,40), and improving neonatal body composition (41,42) as well as placental function (43,44), which results in optimized intrauterine growth conditions.

The Danish Health Authorities recommend that healthy pregnant women are physically active for at least 30 min/day at moderate intensity (45), but only 38% of Danish pregnant women achieve this recommended level (46). Several barriers to PA during pregnancy are addressed in the literature (47), including anxiety about over-doing exercise, low motivation to adopt an active lifestyle during pregnancy, changing energy levels throughout the pregnancy, and lack of time to be physically active (48). The latest recommendations on lifestyle interventions during pregnancy support individualized advice on how to increase the PA level rather than a generic approach (6), as pregnant women prefer personalized information (49). Consequently, policymakers, healthcare professionals, and pregnant women advocate for evidence-based guidance on how to implement PA in everyday life during pregnancy safely and effectively, with approaches that meet the needs, preferences, and choices of the pregnant woman.

During the past decades, many PA intervention studies in pregnant women have been conducted on overweight and obese populations (23,24,26,28,50–57) as well as in healthy normal-weight pregnant women (20,21,32,33,58–61). Still, none of these studies have focused primarily on investigating the effect of the exercise interventions on actual PA level in pregnant women nor have they used novel objective methods to measure actual PA levels. Structured, supervised exercise training and motivational counselling have been applied separately in pregnant women

(20,21,23,24,26,28,32,33,50–55,58–63), but the relative efficacy of these interventions has not been compared; this hampers the evidence-based implementation of effective exercise programs into everyday life.

Objective

This paper describes the protocol of the FitMum study, which is centred around a randomized controlled trial (RCT). The FitMum RCT aims to evaluate the effects of structured supervised exercise training (EXE) and motivational counselling supported by health technology (MOT) compared to standard care (CON) on PA level and body weight gain during pregnancy. Additional aims of the study are to investigate the effects of EXE and MOT on clinical and metabolic health parameters in both mother and offspring. We will also explore how the FitMum exercise programs are carried out and adopted by conducting a process evaluation. In addition, we explore the personal attribution of meaning to the experiences and practices of PA among participants. Furthermore, we investigate how social, structural, and cultural factors facilitate or hinder the successful implementation of exercise during pregnancy.

Methods

Study design

The FitMum RCT is a single-site, three-arm trial study.

Setting

The study is carried out at the Department of Gynaecology and Obstetrics, Nordsjaellands Hospital (NOH), Hillerod, in the Capital Region of Denmark, where approximately 4,000 women give birth per year. NOH is a public hospital and participation in FitMum is free of charge.

Participants

220 healthy, pregnant women are included in this study. Inclusion criteria are an obtained written informed consent, maternal age of 18 years or older, gestational age (GA) of max. 15 weeks, ultrasonic confirmed viable intrauterine pregnancy, body mass index of 18.5-45 kg/m^2 and body weight <150 kg (pre-pregnancy weight or first measured weight in pregnancy), ability to wear a wrist-worn activity tracker 24/7 until one year postpartum and having a smartphone. Exclusion criteria are structured exercise at moderate-to-vigorous intensity for more than one hour/week during early pregnancy, previous preterm delivery, obstetric or medical complications, multiple pregnancies, inability to speak Danish, or alcohol or drug abuse.

Recruitment and inclusion

Participants are recruited 1) *via* booking confirmation of a first-trimester scan, 2) at face-to-face meetings during the first-trimester scan, and 3) through posters, flyers, and social media. Before inclusion, interested women answer an online, one-page pre-screening questionnaire. Eligible participants and their partners are invited to the first visit at NOH as soon as possible and no later than GA of 14 weeks and 6 days. At visit 1, the woman is verbally informed about the study and screened according to in- and exclusion criteria. Women who have not had a first-trimester scan are vaginally

scanned to confirm a singleton, viable intrauterine pregnancy. All eligible women are included and written informed consent is obtained (supplemental file 1). Written informed consent is also obtained from the biological father or other holders of custody as biological samples are collected from the offspring and, if known, from the biological father (supplemental file 2). A short semi-structured interview with the participant is recorded. The interview provides knowledge of the participant's thoughts on participating in a research project, knowledge of prior and current PA level, and experiences with health technologies. After inclusion, anthropometric and demographic information and a blood sample are collected.

At the end of visit 1, the participant receives a commercial activity tracker, Garmin Vivosport. The participant is instructed to wear the tracker continuously 24/7 from the one-week baseline period until one year postpartum, except during charging. The activity tracker is water-resistant and determines the frequency, duration, and intensity of activity periods on a minute-to-minute basis. The data from the activity tracker are wirelessly synced to the associated app, Garmin Connect, provided by Garmin International, and the research platform Fitabase (Small Steps Labs LLC), through which the compliance of wearing and synchronizing the data from the tracker are continuously monitored during the study.

Baseline period and randomization

After inclusion, the baseline PA level of the participant is measured by the activity tracker for one week. After the baseline period, participants are randomized into the CON, EXE, or MOT groups (Figure 1). The target number of participants randomized to each group is 44, 88, and 88, respectively, in order to have more participants in the intervention groups. Randomization is performed via a numbered randomization list administered through the database Research Electronic Data Capture (REDCap), and the investigators are blinded to the procedure. Blinding of participants is considered impossible due to the inherent content of the exercise interventions. The participant is informed about the assigned group by email, and participants in EXE and MOT receive written information containing guidelines from the Danish Health Authorities about PA during pregnancy.

Patient and public involvement

Template for Intervention Description and Replication (64) was used as inspiration for the development and description of the study. As a part of the development phase, stakeholders in the field were involved in discussions and sharing of knowledge. Additionally, 27 semi-structured interviews with Danish pregnant women, midwives, and obstetricians were performed to explore the feasibility of such a study as well as the motivational factors and barriers to PA during pregnancy. Participants are not directly involved in the recruitment and conduct of the study, but a process evaluation is conducted and personal understandings of the participants are obtained via interviews (see below). The insights from the study will be shared with the participants at an information meeting after the end of the study.

Interventions

Standard care at the hospital

All three groups are offered the standard care that applies to women giving birth at NOH. This consists of three appointments with their general practitioner (GA week 6-10, 25 and 32), five to six midwife consultations (GA week 14-17, 29, 36, 38, 40 and if still pregnant around week 41 as well) and ultrasonic scans at GA week 12 and 20.

Standard care control group (CON)

Participants in CON wear an activity tracker to determine their activity level. The face of the tracker looks like a normal watch showing only time and battery life.

Structured supervised exercise training intervention (EXE)

The targeted PA level for all participants in EXE and MOT is at least 30 min/day at a moderate intensity as recommended to healthy pregnant women (6) and all participants are informed hereof if randomized to EXE or MOT. In EXE, exercise training takes place in teams and is supervised by health professionals (exercise physiologists, physiotherapists, public health scientists). It consists of three weekly one-hour exercise sessions at moderate intensity, including two exercise sessions in a gym and one in a public swimming pool. The gym sessions consist of a combination of aerobic and resistance training with 30 min stationary bike training (a combination of hill climbing and high cadence intervals) and 30 min of other exercise, e.g. elastic bands, exercise balls, mats, dumbbells or body weight. In the swimming pool, participants do 15 min of swimming and 45 min of water exercises with plates, balls, dumbbells or body weight. Moderate intensity during training sessions is assessed using both heart rate monitoring of 65-80% of age-predicted maximal heart rate (from the activity tracker) and perceived exertion in the range of 12-14 on Borg's conventional 6-20-point scale (64), as recommended by the American College of Obstetricians and Gynaecologists (14). If a participant experiences any pain or needs to slow down, the content of exercise sessions (repetitions and/or resistance) is individually adjusted accordingly. Special attention is paid to the newly recruited participants. Exercise sessions are offered at seven different times per week, and participants are recommended to sign up for three of these sessions. The sessions are held early mornings or late afternoons all weekdays, and before noon on Fridays and Saturdays.

Motivational counselling supported by health technology (MOT)

This intervention is comprised of four individual and three group counselling sessions as well as weekly SMS-reminders. The overall focus of both the individual and group counselling sessions is based on what already motivates the participants to increase or maintain their PA level. The motivation technique applied is inspired by motivational interviewing (65), self-determination theory (66), and behaviour change techniques (67).

All four *individual sessions* last one hour and are led by professional health counsellors (exercise physiologists, physiotherapists, public health scientists). The sessions aim to discuss the participant's

barriers, wishes, needs, knowledge, and former PA experiences to identify individual characteristics and motivation towards a more physically active lifestyle. Aside from measuring the PA level, the activity trackers are also used as an intervention element to motivate the participants to increase their PA levels (68). During individual sessions, feedback on recent PA performances is provided based on activity data acquired from the activity tracker, in order to give the participants insight into their PA level. The participants will, with guidance from the counsellor, set their own activity goals and make an individual action plan to increase the PA level, which may have a motivating effect on PA behaviour (68,69). Individual sessions are scheduled during the daytime as conveniently for the participant as possible.

The first *group session* lasts one hour and aims to inform the participants about guidelines for PA, benefits associated with PA during pregnancy, and possible ways to increase PA during pregnancy. In the following two two-hour group sessions, the interaction between the participants is used to create meaningful group processes such as support, experience exchange, reflection, learning, and development. These sessions focus on the discussion of relevant topics concerning PA during pregnancy, and the counsellor acts as a facilitator through the session, with the topics of conversation chosen by the participants. Issues like postpartum PA, the pelvic floor, uterine contractions, diastasis recti, and myths about pregnancy PA are discussed. Group sessions are held late afternoons, or before noon for those on maternity leave.

The weekly SMS-reminders have supportive and motivating content and are used to encourage the participants to achieve a moderate PA level. The texts are chosen based on every participant's PA level during the last week measured by the activity tracker. One example of the text: "You have been exercising regularly for an extended period of time. Well done. Good habits make it easier for you to continue as your belly gets bigger and heavier."

Outcome measures

The data collection procedures are illustrated in Table 1.

Primary outcome: physical activity level

The primary outcome of FitMum RCT is min/week of moderate-to-vigorous-intensity PA measured continuously from randomization to GA of 28 weeks and 6 days as determined by a wrist-worn activity tracker, Garmin Vivosport, with a built-in heart rate monitor and accelerometer.

Secondary outcome: gestational weight gain

Body weight of the participant before pregnancy is self-reported. The body weight during pregnancy is measured five times from inclusion until delivery on the same scale (Seca 799) with the participant in light clothes and without shoes.

Additional outcomes

Complementary measures of physical activity

Complementary measures of PA are obtained by the Danish version of 'Pregnancy Physical Activity Questionnaire' (PPAQ) (70) named PPAQ-DK, and by the doubly labelled water technique (71). PPAQ is a semi-quantitative and subjective instrument, which has been validated (70) and is considered one of the most valid and reliable questionnaires for the assessment of PA level in pregnant women (72). Our research group has translated PPAQ to Danish and validated it in a Danish pregnant population (73).

The doubly labelled water technique is the 'gold standard' technique to measure free-living energy expenditure objectively, and is safe, even for pregnant women, as it relies on stable, non-radioactive isotopes (74–77). The participants are administered a glass of water for oral intake containing 0.1 g of 99.98 % $^{2}H_2O$ and 1.6 g of 10% ^{18}O per kg body weight. In total, five post-dose urine samples are collected in the morning (not the first urine void of the day); on the day after oral water dosage, and after four, seven, 11, and 14 days. The urine samples are stored in the participant's freezer and later at -80 °C.

In addition, the PA of the participants is determined from GA week 29 until delivery and in the first year postpartum by the activity tracker. The measures of PA include active calories, active time, steps, heart rate, moderate- and vigorous-intensity activity, floors climbed, MET-min/week, and type of activity, which is recognized automatically by the tracker.

Clinical and psychological health parameters in participant, partner, and offspring

A variety of clinical and psychological health parameters are obtained from the participant, her partner, and her offspring. *Clinical data* regarding pregnancy, delivery, and neonatal outcomes are collected from medical records. *Health-related quality of life* is determined in the participant by the Danish version of the Medical Outcomes Study Short Form 36 (SF-36) (78,79), which has also been validated in pregnant women (80). *Exercise self-efficacy* is determined by the Danish version of the Pregnancy Exercise Self-Efficacy Scale (P-ESES) (81). P-ESES has been translated into Danish and validated in a Danish pregnant population by our research group (82). *PA motivation* is determined by the Danish version of the Behavioural Regulation in Exercise Questionnaire (BREQ-2) (83–85), which is the most widely used measure of the continuum of behavioural regulation in exercise psychology research. *Sleep quantity and quality* are assessed in the participant by the activity tracker and by the Danish version of the self-administered questionnaire Pittsburgh Sleep Quality Index (PSQI) (86,87). The PSQI is considered a valid and reliable tool to assess sleep metrics among pregnant women (88). In addition, a validation of activity trackers to measure sleep will be conducted using polysomnography in a sub-group of women already participating in the FitMum study. *Sick leave and pelvic and low back pain* are registered by asking the participant whether she has been absent from work/study and on sick leave during her pregnancy and whether she has experienced pelvic and/or low back pain before and during her pregnancy. *Maternal body composition* is determined from total body water measured by doubly labelled water technique and by a postpartum Dual-energy X-ray absorptiometry (DXA) scan.

Offspring growth: Head circumference, length, and weight is measured at birth, and by general practitioners at five weeks, five months, and 12 months postpartum. Participants receive an electronic questionnaire and fill out the anthropometric data along with information on offspring dietary habits and vaccine-status. *Parental mental wellbeing* is assessed 6-8 weeks after birth. Both parents or holders of custody receive a questionnaire consisting of the Edinburgh Postnatal Depression Score, and Gotland Depression Scale which are combined as a screening tool for postnatal depression (89–92) in Danish postnatal care. *Psychomotor development of the offspring* is assessed by the validated Ages and Stages Questionnaire 3 (ASQ-3), which is administered electronically to participants 12 months after the due date. ASQ-3 pinpoints developmental progress in the fields of communication, gross motor, fine motor, problem-solving, and personal-social skills. The administration of ASQ-3 relative to due and not to birth date aims to correct for variance in cognitive and motor skills due to premature birth. *Offspring physical activity* is assessed for seven days by an infant activity tracker (Actigraph GT3X+) 12 months after the due date. The tracker detects level, intensity, and pattern of physical activity.

Analyses of blood, placenta and breast milk samples

Plasma metabolites and hormones are assessed in maternal and paternal venous blood. The blood samples will be analysed for concentrations of glucose, cholesterol (total, high and low density), triglyceride, insulin, free fatty acids, amino acids, interleukin-6, and C-reactive protein. Venous blood is obtained from the umbilical cord within 30 min after delivery of the placenta. The blood will be analysed for concentrations of glucose, cholesterol (total, high and low density), triglyceride, insulin, c-peptide, free fatty acids, amino acids, adiponectin, and leptin. Furthermore, epigenetic profiling at the level of *DNA methylation* will be performed in maternal, paternal, and umbilical cord blood mononuclear cells. Bioinformatic comparison of DNA methylomes from parents and offspring will infer on the DNA methylation marks that are modulated by maternal exercise and transmitted to the offspring. Information on DNA methylomes from each parent will allow us to distinguish between maternally and paternally epigenetic profiles transmitted to the offspring. Principal component analyses will be used to identify the specific metabolic or anthropometric features of the mother that are associated with a specific DNA methylation footprint transmitted to the offspring. *Placental function* is assessed from samples taken within 30 min after delivery of the placenta. The samples are immediately frozen on dry ice and stored at -80 °C. Analyses will include RNA-seq, non-targeted metabolomics, RT-qPCR, Western blot, histology, and immunohistochemistry. *Breast milk* is obtained from a single feed at the day of visit 5 and stored at -80 °C for later metabolomic and lipidomic analyses.

Process evaluation of interventions

A process evaluation is made using quantitative and qualitative methods to provide insight into mechanisms through which interventions bring about change, assess fidelity and quality of implementation, clarify causal mechanisms, and identify contextual factors associated with variations in outcomes (93–95). Integrating process evaluations alongside outcome data is recommended by the UK Medical Research Council guidelines in order to develop and evaluate complex interventions to improve the interpretation of the outcomes, design more effective interventions, and apply

interventions appropriately across groups and settings by understanding the implementation and functioning of interventions in a given context (94,96). The RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework is used to improve reporting on key issues related to the implementation and external validity of FitMum RCT (97).

Personal understandings of physical activity

The qualitative dataset is comprised of 220 short standardised screening interviews, 30 semi-structured interviews, 70 observations, five sets of auto-ethnographies, visual material, as well as drop-out and follow-up interviews. This sub-project will explore the physical and mental health and wellbeing of the participants, their social relations, PA levels, and their experience of pregnancy to identify the challenges and barriers of PA during pregnancy. Personal understandings of PA in the everyday life of participants are determined at inclusion, GA week 34, and one year postpartum, in approximately ten participants from each of the three study groups.

Changes during the COVID-19 pandemic

Due to the COVID-19 pandemic (present in Denmark from March 11th 2020), supplies of interventions (EXE and MOT) and visits are periodically changed. During the lockdown periods in spring and autumn 2020, all interventions and visits (except birth) are converted into online versions using Zoom Cloud Meetings or telephone. In EXE, the swimming pool sessions are replaced with online land exercises. From March 11th 2020, all land exercise sessions consist of 30 min of aerobic exercise where the participants exercise on their own (e.g. biking, power-walking, dancing, aerobics) followed by 30 min of supervised online group resistance training. All individual and group MOT sessions are held online.

As much data as possible is collected during the pandemic, but some clinical data have not been possible to obtain in all participants due to limitations on non-urgent visits to the hospital. No blood samples are obtained at the virtual 'visits', women are weighed at home, and symphysis-fundal height measurements are not obtained. No doubly labelled water is administered at the virtual 'visit' 2. The participant's body weight at visit 4 is noted by the midwives on the day of giving birth, but biological samples are not collected. No DXA-scans or breast milk samples are collected at 'visit' 5.

Data management and analysis

Data management

The activity tracker data are collected by Fitabase, which regularly backs up the data. A participant who does not synchronize the tracker for seven days or more is reminded by email, text message, or phone call. All tracker data are exported from Fitabase to R (98) for data analysis. Tracker data are utilized to calculate non-wear time; a week is included in the analysis if the week has four or more days with complete data. A day that has six hours or more of non-wear time is excluded and considered a missing day. An electronic case report form (e-CRF) is utilized to collect all clinical data related to the trial. Data are stored in coded form according to the rules of the Danish Data Protection Agency. Personal data processing complies with the Act on Processing of Personal Data. Data is owned by

NOH and University of Copenhagen. Use of data generated in FitMum RCT in new contexts must be agreed and approved by the Steering group. Technical University of Denmark and Aarhus University must have access to the data they have collected and are free to use it in new contexts. The e-CRF is completed by the investigators at the time of the participant's visits at NOH so that it always reflects the latest observations of the participant. Data will be stored for 25 years, after which they will be transferred to the Danish National Archives "Rigsarkivet" in an anonymized format.

Sample size

FitMum RCT has been powered to detect an overall significant difference in the primary outcome between the three groups as well as a significant difference between the two intervention groups (EXE vs. MOT) with average activity levels of 60 (CON), 210 (EXE) and 150 (MOT) min/week. The standard deviation was set at 116 min/week and based on the results from Oostdam et al. (51). The required sample size is determined to obtain a power of 80% with a family-wise significance level of 5%. The sample size calculation showed that the required number of participants is 35 in CON and 70 in each of the two intervention groups due to the randomization ratio of 1:2:2 to CON, EXE, and MOT, respectively. Based on an expected lost-to-follow-up rate of 20%, as seen in similar exercise studies in pregnant women (28,32,33,51), we plan to include 44 participants in CON and 88 participants in each of the two intervention groups, making a total of 220 participants.

Statistical methods

Data analyses of both primary and secondary outcomes will be performed using intention-to-treat analyses. In addition, a dose-response model will be estimated to quantify the relationship between adherence to the intervention (proportion of attendances in the planned EXE and MOT sessions, respectively) and the activity level. Moreover, analyses describing associations between the level of physical activity (as measured by the activity tracker) and the secondary and additional outcomes will be performed. Baseline data will be reported as averages and standard deviations (medians and interquartile ranges) or frequencies and proportions as appropriate. No interim analyses will be performed on the primary and secondary outcomes. The analysis of the primary outcome will be performed using a linear model with the randomization group as a categorical covariate and with adjustment for baseline PA level. Hypothesis tests will be performed using likelihood ratio tests. Statistical analysis will be conducted using R (98). Analyses of the primary outcome will be performed by a statistician blinded from the intervention allocations. Investigators will perform analyses of baseline data and secondary and additional outcomes under the supervision of a statistician. A full statistical analysis plan is published in clinicaltrials.gov (99).

Trial status

The recruitment of participants began in September 2018 and ended in October 2020. Data collection of the primary outcome is expected to be complete in spring 2021. Full data collection is expected to be complete in 2022.

Ethics and dissemination

The FitMum study adheres to the principles of the Helsinki declaration. The study is approved by the Danish National Committee on Health Research Ethics (# H-18011067) and the Danish Data Protection Agency (# VD-2018-336).

All participants consent in written form before inclusion and are informed that participation in the FitMum study is voluntary. Participants are informed that they may withdraw from the study at any time, and that withdrawal of consent will not affect any subsequent pregnancy and delivery processes at NOH. The participant has time to ask questions and is allowed 24 hours to deliberate on study participation before the obtainment of written informed consent.

FitMum RCT is designed based on recommendations of appropriate PA during pregnancy (14,45,100,101), and although anatomic and physiological changes occur during pregnancy, PA during an uncomplicated pregnancy is safe (14,22,29,40,60,102–105). All information about adverse events and serious adverse events are documented consecutively and will be reported. Participants will be discontinued from the intervention if they are at risk of preterm birth, if a cervical length below 25 mm is measured, if serious obstetric or medical complications occur, if investigators' assessment reveals that continuation in the trial would be detrimental to the participant's well-being, or if intolerable adverse events occur.

The FitMum study will provide evidence-based knowledge that can contribute to improving national and international recommendations of PA during pregnancy and to new, effective, and simple guidance to implement health technology-supported exercise programs to pregnant women. Based on the results and process evaluation, the knowledge and tools from the FitMum study can be transformed into initiatives in municipalities and hospitals to improve the health and quality of life for both mother and child, and can be used for preventing the development of lifestyle-related diseases across generations.

Findings will be submitted for publication in peer-reviewed scientific journals and disseminated at national and international conferences. In addition, results will be disseminated to the public in relevant media and to health professionals via science theatre performances.

Discussion

The FitMum study aims to evaluate the effects of structured supervised exercise training and motivational counselling supported by health technology on PA level during pregnancy to generate evidence about *how* to implement PA in everyday life in healthy pregnant women. Previous studies have investigated the effect of different lifestyle interventions on various health outcomes in normal weight (23,24,26,28,50–57), overweight, and obese pregnant women (20,21,32,33,58–61). However, none of these studies have focused primarily on investigating the effect of PA interventions on actual PA level determined by novel objective methods. In addition, the FitMum study compares the effect of two very different PA interventions to explore strategies to implement PA programs into pregnant women's everyday life. Moreover, offspring of FitMum participants will be studied for one year after

birth, whereby knowledge on the effect of PA during pregnancy on offspring health will be obtained. A limitation of the study is that the true effect of motivational counselling is not identified, as technology is an integral part of the MOT intervention.

Consumer-based wearable activity trackers tend to increase PA level when they are used as an intervention tool or as part of an intervention (106). Activity trackers are often relatively light weight, comfortable to wear, and rechargeable (107). In addition, using an activity tracker to measure PA during pregnancy is feasible, recommended (108), and has a reasonable compliance rate during pregnancy and after giving birth (109). However, there are some challenges and limitations of using activity trackers in a long-term intervention study. Firstly, the participants must recharge the device and synchronize their data approximately once per week, which burdens participants and challenges adherence and compliance. Secondly, we cannot control the interaction of CON participants with the tracker. Thirdly, the main goal for the tracker's design is a comfortable wear, yet wearing the tracker for extended periods of time may cause skin irritation and discomfort (110). Moreover, the unavailability of the raw data and algorithms used by the manufacturer creates a limitation in the validation of PA metrics (107). Therefore, measuring PA by a variety of methods, and comparing these methods with the doubly labelled water technique (a gold standard method), will be used in order to obtain comprehensive measures of PA behaviours in FitMum participants.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Authors' contribution

BS initiated the FitMum study together with LT and is the principal investigator of FitMum RCT. EL is the clinical trial manager. A steering group consisting of BS, EL, TDC, JEL and HTM oversees trial status and progression. CBR, SdPK and BS led the protocol development with contribution from SA, ADA, JB, TDC, SM, AKJ, GT, APJ, JEL, GvH, EA, RB, OHM, HTM, LT, and EL. CBR, SdPK, SA, ADA, JB, TDC, SM, EL and BS constitute the clinical core group that guides the practical performance of FitMum RCT. CBR, SdPK and ADA conduct intervention activities together with research assistants and master's students. CBR, SdPK, SA and ADA will perform most of the data analysis along with

AKJ. Analyses of the primary outcome will be performed by AKJ. All authors read, contributed to and approved the final version of the manuscript.

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Table 1: Procedures and measurements used in the FitMum study

Visit number Gestational age (week+days)	Visit 1 Screening and baseline testing Max. 15+0	E-mail Randomization One week after inclusion	Visit 2 Week 28+0-6	Visit 3 Week 34+0-6	Visit 4 Delivery Approximately week 40	Visit 5 7-14 days after delivery	 One year after delivery
Ultrasound scan	x						
Verbal information about study	x						
Medical interview to assess in- and exclusion criteria	x						
Demographic and anthropometric data	x						
Medical history, concomitant disease, and previous medication	x						
Medical history, PA level, demographic and anthropometric data of the participant's partner	x						
Written informed consent	x						
Activity tracker and associated oral and written information	x						
Randomization		x					
METHODOLOGY FOR OBTAINING ENDPOINTS							
Activity tracker	Continuously during the trial and one year after delivery						
Maternal body weight	x		x	x	x	x	Six times at home

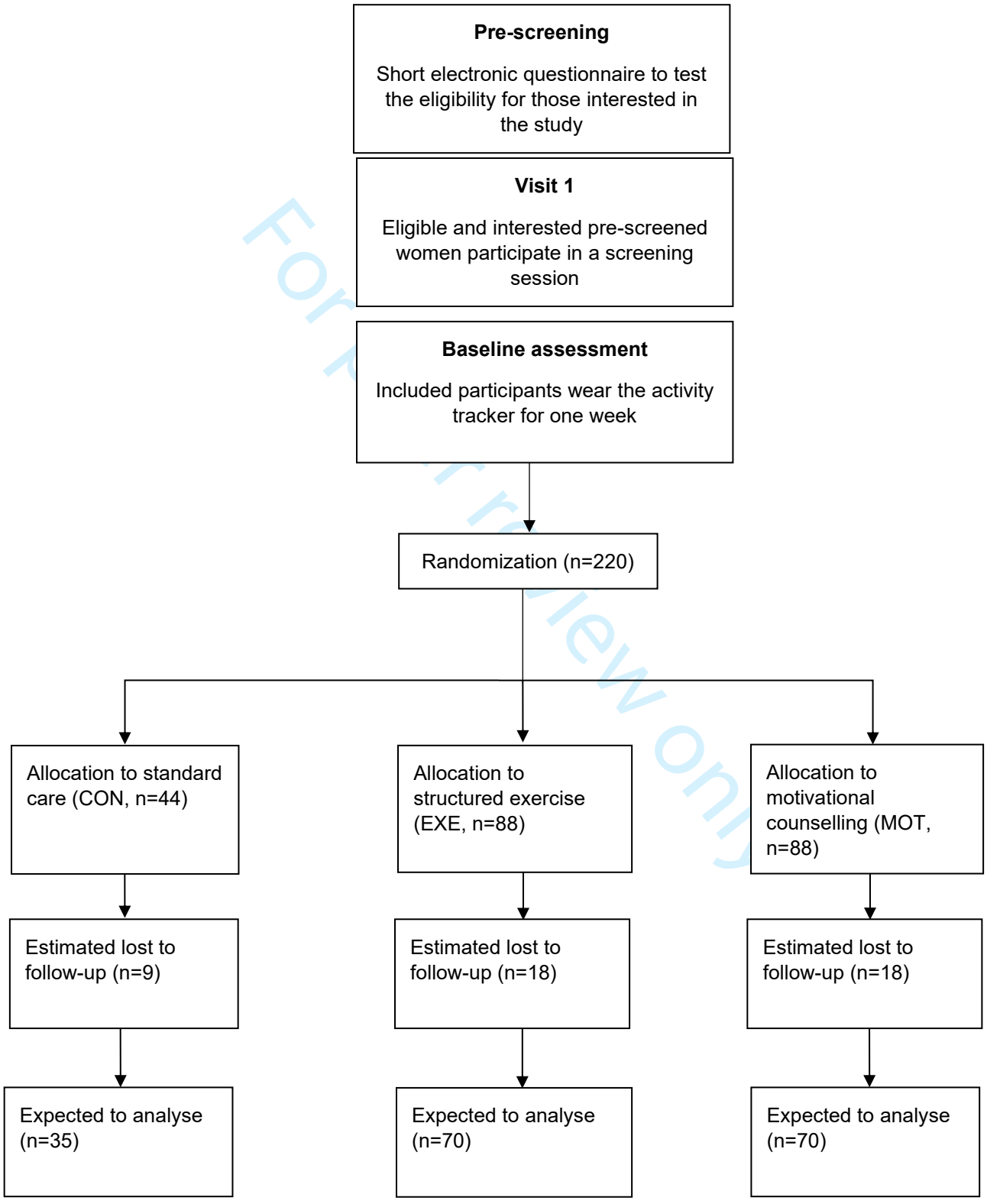
							during postpartum
Doubly labelled water			x				
Questionnaires: PPAQ-DK, SF-36, PSQI, P-ESES, BREQ-2, sickness absence + pelvic and low back pain	x		x	x			x
Maternal blood samples	x		x	x	x		
Paternal blood sample					x		
Umbilical cord blood sample					x		
Placenta samples					x		
DXA-scan						x	
Breast milk sample						x	
Qualitative interview	x			x			x
Observation and autodocumentation		Recurring					
ASQ-3							x
Growth assessment at general practitioner							5 weeks, and 5 and 12 months
Parental mental well-being questionnaire							6-8 weeks postpartum
Seven-day child accelerometer							x
SAFETY							
Record adverse events			x	x			
Symphysis-fundal height			x	x			

ASQ-3: Ages and Stages Questionnaire 3, BREQ-2: Behavioural Regulations Exercise Questionnaire, DXA: Dual-energy X-ray absorptiometry, P-ESES: Pregnancy Exercise Self-efficacy Scale, PPAQ-DK: Pregnancy PA Questionnaire (Danish version), PSQI: Pittsburgh Sleep Quality Index, SF-36: The Medical Outcomes Study Short Form 36.

Figure legends

Figure 1: Flow diagram of the FitMum randomized controlled trial

Figure 1: Flow diagram of the FitMum randomized controlled trial.



Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt

Forskningsprojektets titel: FitMum

Erklæring fra projektdeltageren:

Jeg har fået skriftlig og mundtlig information og ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage i FitMum.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage, uden at det vil få konsekvenser for mit videre graviditets-, fødsels- og barselsforløb på Nordsjællands Hospital.

Jeg giver samtykke til at deltage i forskningsprojektet, og har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Navn: _____

E-mail: _____

Telefonnummer: _____

Dato: _____ Underskrift: _____

Ønsker du at blive informeret om forskningsprojektets resultater samt eventuelle konsekvenser for dig?

Ja _____ (sæt x) Nej _____ (sæt x)

Ønsker du at blive informeret om væsentlige helbredsmæssige fund hos dig?

Ja _____ (sæt x) Nej _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at projektdeltageren har modtaget mundtlig og skriftlig information om projektet.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i projektet.

Navnet på den, der har afgivet information: _____

Dato: _____ Underskrift: _____

09.05.2018 – version 3. Anmeldelsesnummer Videnskabsetisk Komité: 61462.

Informeret samtykke fra forældremyndighedsindehaver(e) til barns deltagelse

i et sundhedsvidenskabeligt forskningsprojekt

samt

informeret samtykke fra biologisk faders deltagelse

i et sundhedsvidenskabeligt forskningsprojekt

Forskningsprojektets titel: FitMum

Erklæring fra indehaver(e) af forældremyndigheden til barns deltagelse:

Jeg/vi har fået skriftlig og mundtlig information og ved nok om formål, metode, fordele og ulemper til at give mit/vores samtykke til mit/vores barns deltagelse i FitMum. Jeg/vi ved, at det er frivilligt at deltage, og at jeg/vi altid kan trække mit/vores samtykke tilbage, uden at det vil få konsekvenser for det videre graviditets-, fødsels- og barselsforløb på Nordsjællands Hospital.

Jeg/vi giver samtykke til, at mit/vores endnu unavngivne barn deltager i forskningsprojektet, og at der i forbindelse med fødslen udtages navlesnorsblod og moderkagevæv, der opbevares i en forskningsbiobank, samt at overskydende biologisk materiale overføres til en biobank til fremtidig forskning. Jeg/vi har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Navnet på forældremyndighedsindehaver a: _____

Dato: _____ Underskrift: _____

Navnet på forældremyndighedsindehaver b: _____

Dato: _____ Underskrift: _____

Ønsker du/I at blive informeret om forskningsprojektets resultater samt eventuelle konsekvenser for dit/jeres barn?

Ja _____ (sæt x) Nej _____ (sæt x)

Ønsker du/I at blive informeret om væsentlige helbredsmæssige fund hos dit/jeres barn?

Ja _____ (sæt x) Nej _____ (sæt x)

03.12.2018 – version 5. Anmeldelsesnummer Videnskabsetisk Komité: 61462.

Erklæring fra biologisk fader til egen deltagelse:

Jeg (biologisk fader) har fået skriftlig og mundtlig information og ved nok om formål, metode, fordele og ulemper til at give mit samtykke til at deltage i FitMum.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage, uden at det vil få konsekvenser for det videre graviditets-, fødsels- og barselsforløb på Nordsjællands Hospital.

Jeg (biologisk fader) giver samtykke til at deltage i forskningsprojektet og til, at mit biologiske materiale (blod) opbevares i en forskningsbiobank, samt at overskydende biologisk materiale (blod) overføres til en biobank til fremtidig forskning. Jeg har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Navnet på den biologiske fader: _____

Dato: _____ Underskrift: _____

Ønsker du (biologisk fader) at blive informeret om forskningsprojektets resultater samt eventuelle konsekvenser for dig?

Ja _____ (sæt x) Nej _____ (sæt x)

Ønsker du (biologisk fader) at blive informeret om væsentlige helbredsmæssige fund hos dig?

Ja _____ (sæt x) Nej _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forældremyndighedsindehaver(e) har modtaget mundtlig og skriftlig information om projektet.

Efter min overbevisning er der givet tilstrækkelig information til, at forældremyndighedsindehaver(e) kan træffe beslutning om henholdsvis dit/deres barns og faderens deltagelse i projektet.

Navnet på den, der har afgivet information: _____

Dato: _____ Underskrift: _____

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

NA= not applicable

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 14
	5b	Name and contact information for the trial sponsor	14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4&5
	6b	Explanation for choice of comparators	4&5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5 & 12
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7&8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7,8 & 11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	23&24
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5&6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11&12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 12&13
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplemental Material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Table 1 and (page 9 &10)

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