Statistical Analysis Plan (SAP) for the FitMum randomized controlled trial

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Contents

Section 1: Administrative

Title

FitMum randomized controlled trial. Acronym: FitMum RCT.

Trial registration number

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SAP version 1

Protocol version

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Persons writing the SAP and their roles and responsibility

Name	Title	Role	Signature	Date
Bente Merete Stallknecht [1]	Professor, MD, PhD, DMSc	Wrote the SAP, wrote the study protocol, Principal Investigator		15.07.20
Ellen Christine Leth Lokkegaard [2,3]	Professor, Chief Physician, Department of Gynecology and Obstetrics	Wrote the SAP, wrote the study protocol, Co-Investigator		11.7.20
Stig Molsted [4]	Associate Professor, Senior Researcher, PhD	Wrote the SAP, wrote the study protocol, Co-Investigator		21.7.20
Andreas Kryger Jensen [4,5]	Associate Professor	Wrote the SAP, wrote the study protocol, responsible statistician		10/07-2020
Saud Alomairah [1,3]	PhD student	Wrote the SAP, wrote the study protocol, Co-Investigator		21.07.2020
Caroline Borup Roland [1,3]	PhD student	Wrote the study protocol, Co-Investigator		20.07.2020
Signe de Place Knudsen [1,3]	PhD student	Wrote the study protocol, Co-Investigator		07.07.2020
Jane Bendix [3]	RM, Post Doc, MSc, PhD	Wrote the study protocol, Co-Investigator		15.07.20
Tine Clausen [2,3]	Associate Professor, PhD, Chief Physician	Wrote the study protocol, Co-Investigator		9/7-2020

Affiliation

[1] University of Copenhagen, Department of Biomedical Sciences, Copenhagen, Denmark
[2] University of Copenhagen, Department of Clinical Medicine, Copenhagen, Denmark
[3] Nordsjællands Hospital, Department of Gynecology and Obstetrics, Hillerød, Denmark
[4] Nordsjællands Hospital, Department of Clinical Research, Hillerød, Denmark
[5] University of Copenhagen, Department of Public Health, Biostatistics, Copenhagen, Denmark

Section 2: Introduction

Background and rationale

Pregnancy can be a great chance to implement good habits, such as physical activity, as pregnant women are in regular contact with health professionals and may be motivated to adopt healthy

behaviors as evidenced by reduced alcohol consumption and smoking cessation [1–3]. Structured supervised exercise training and motivational counseling constitute two very different approaches to implement and maintain a physically active lifestyle. Both approaches have been applied separately in pregnant women [4–23], but the relative efficacy of structured supervised exercise training and motivational counseling has not previously been compared in pregnant women. In the FitMum randomized controlled trial (RCT), we will test the efficacy of two exercise approaches versus a control group on physical activity level, which will be measured objectively by a consumer activity tracker in all three trial groups. The two exercise programs are structured supervised exercise training (EXE) and motivational counseling (MOT), respectively. The control group (CON) will receive usual care.

Objectives and hypotheses

Primary objective

- The primary objective is to investigate the effects of EXE and MOT on moderate to vigorous physical activity (MVPA) in pregnant women.
  The hypotheses are:
  1. EXE is more effective than MOT to increase MVPA in pregnant women
  2. MOT is more effective than usual care (CON) to increase MVPA in pregnant women.

Secondary objective

- The secondary objective is to investigate the effects of EXE and MOT on gestational weight gain (GWG).
  The hypotheses are:
  1. Pregnant women in the EXE group gain less weight than those in the MOT group
  2. Pregnant women in the MOT group gain less weight than those in the CON group.

Exploratory outcomes

- Complementary data on levels of physical activity are determined using doubly labeled water, questionnaires, and additional data from the activity tracker.
- Clinical and metabolic health parameters in mother and offspring.

Section 3: Study Methods

Trial design

Single-site three-armed randomized controlled trial.

Brief description of the interventions

The targeted physical activity level for all participants in the EXE and MOT groups is at least 30 minutes per day at moderate intensity as recommended to healthy pregnant women [6].

Standard care control group (CON)

The CON group is offered standard care at the hospital.

Structured supervised exercise training (EXE)

The training is performed in groups and supervised by health professionals. It consists of three weekly one-hour exercise sessions at a moderate intensity, including two land exercise sessions and one water exercise session.

Motivational counseling supported by health technology (MOT)

This intervention comprises four individual and three group counseling sessions during the pregnancy as well as weekly SMS-reminders. The overall focus of both the individual and group counseling sessions is to create a climate that taps into what already motivates the participants to increase or maintain their physical activity level. The activity trackers are used as an intervention element to motivate the participants to increase their physical activity levels. The weekly SMS-reminders have supportive and motivating content and are used to encourage the participants to achieve a moderate physical activity level.

Changes of the intervention during the COVID-19 pandemic

During the COVID-19 pandemic, EXE is converted to exercise at home with online group sessions. MOT is also held online. As much data as possible will be collected during the pandemic, but some clinical data may not be possible to obtain.

Randomization

After a one-week baseline period where the physical activity level is measured by the activity trackers, the women are randomly assigned in a 1:2:2 ratio to CON, EXE or MOT. The randomization is performed via a numbered randomization list administered through the electronic database REDCap and the investigators are blinded to the randomization procedure.

Sample size

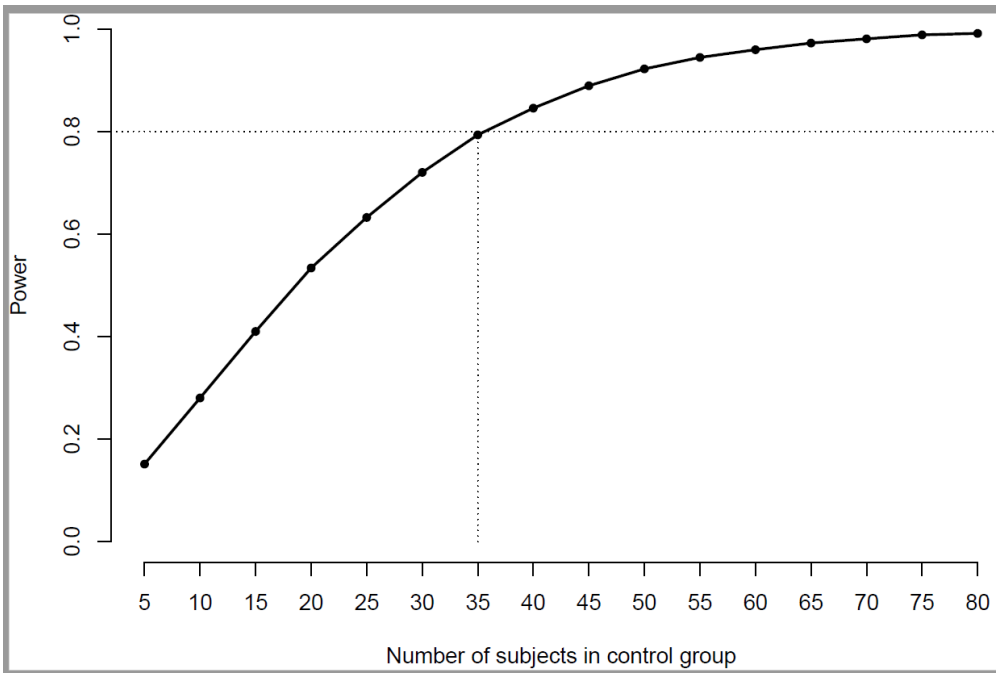
Primary outcome

The sample size has been calculated for physical activity level among pregnant women from randomization to GA week 28+6. We consider a scenario with a comparison of three groups (CON, EXE and MOT). It is assumed that the two interventions have a positive effect, and we stipulate that the average activity levels in the three groups are 60, 210 and 150 min/week, respectively. The stipulations are based on the participants in the intervention groups reaching the target of being physically active for at least 30 min/day (7 x 30 min/day = 210 min/week). Also, we would like to be able to detect a difference in the weekly activity level of 60 min/week. Therefore, an activity level of 150 min/week is stipulated in one of the intervention groups. Lastly, the activity level in CON is stipulated to be 60 min/week as structured exercise at moderate to vigorous intensity for more than one hour/week is an exclusion criterion. Based on a literature study [10], we estimate that the standard deviations in the three groups are the same and equal to 116 min/week. We assume that data are normally distributed. We require a power of 80%.

We consider the alternative hypothesis that the average activity levels in the three groups are significantly different from each other and the average activity levels in the two intervention groups are also significantly different from each other (a double hypothesis). We calculate the required sample size by simulation using a likelihood ratio test at a joint significance level of 5% for the two hypotheses

using a Bonferroni correction. We choose to randomize to the ratio 1:2:2 (CON:EXE:MOT) as this requires the lowest number of participants, and gives the participants (who we assume are motivated for being more physically active) the greatest chance of being randomized to an intervention group. In order to obtain the required power, 35 participants in the CON group and 70 participants in EXE and MOT groups are required, and hence 175 participants in total (Figure 1).

Figure 1: Overview of the sample size of participants needed in the control group to reach a strength of 80 %, considering scenario characterized by having the double number of people in each intervention group relative to the number in the control group (2:2:1 randomization).



The expected lost-to-follow-up rate needs to be considered and added to the sample size. Therefore, we will include 44 participants in CON and 88 participants in EXE and MOT, respectively, in total 220 women, based on an expected lost-to-follow-up rate of 20%, as seen in similar exercise studies in pregnant women [6,10,12,19]. This should leave 35 participants in CON (0.8 x 44) and 70 participants in each of the two intervention groups (0.8 x 88), which will give sufficient power for analysis of the primary outcome.

Secondary outcome

Based on a comparable intervention study with exercise training [21], the estimated GWG in the intervention and control groups had standard deviations of 4 kg. Thus, in the present study, 33 women in the CON and 66 in each of the intervention groups (EXE and MOT) are needed to detect a difference of 2.8 kg between the control and the intervention groups with a power of 0.80 and two-sided α-level of

0.05. The sample size calculation to this secondary outcome was performed during the intervention but before the intervention was completed.

Framework

The hypothesis testing framework is based on model comparisons using the Likelihood Ratio Test of equality between null and alternative models.

Statistical interim analyses

No interim analyses will be performed. The trial will not be stopped early as a result of data analyses.

Timing of final analysis

The final analysis of the primary outcome will be performed when the last participant has passed GA week 28+6. The final analysis of the secondary outcome will be performed when the last participant gives birth.

Timing of outcome assessments

The primary outcome is measured continuously (24/7) from randomization to GA week 28+6. The secondary outcome is measured at baseline (max. GA week 15+0), GA week 28+0-6, GA week 34+0-6 and at delivery.

Section 4: Statistical Principles

Confidence intervals and P values

The level of statistical significance is 5%. The primary analysis containing two hypotheses will be tested at a significance level of 2.5% each to control the family-wise type I error. Wald-based 95% confidence intervals will be given for all reported estimates.

Adherence, protocol deviations, and analysis populations

The primary analysis is an intention-to-treat analysis including all participants as randomized. Also, a dose-response model will be fitted for the EXE and MOT groups to describe the relationship between adherence to the intervention (proportion of attendances) and the attained activity level. This relationship will be compared to the average activity level in the CON group.

Section 5: Trial Population

Screening data

Screening data will not be reported.

Eligibility

Inclusion criteria

- Written informed consent obtained before any trial-related procedures are performed
- A pregnant woman aged 18 years or older
- GA of max. 15+0 weeks
- Ultrasonic confirmed intrauterine pregnancy
- BMI of 18.5-45 kg/m^2 and body weight below 150 kg calculated from pre-pregnancy weight or first measured weight in pregnancy

- Ability to wear a wrist-worn activity tracker 24/7

Exclusion criteria

- Severe chronic disease
- Structured exercise at moderate to vigorous intensity more than 1 hour per week during pregnancy
- Previous preterm delivery (before GA week 37)
- Obstetric or medical complications
- Multiple pregnancies
- Non-Danish speaking
- Alcohol or drug abuse

Recruitment

The flow chart of the trial will follow the CONSORT guidelines and will include the number of individuals who a) showed interest to participate in the study by filling out a pre-screening questionnaire, b) were assessed for eligibility at screening visit, c) were included in the trial, d) were randomized, e) did not receive allocated treatment, f) were lost to follow-up, g) discontinued the intervention, and h) were analyzed in the end.

Withdrawal/lost to follow-up

If a randomized participant withdraws or is discontinued from the intervention, we will offer to perform all or some of the planned visits. The number/frequency of participants lost to follow-up will be provided for each group and for each visit. If possible, the reasons for participants not completing the trial will be given. Summary of baseline levels for variables reported in the baseline table will be provided for completers and non-completers.

Baseline patient characteristics

Categorical variables will be summarized by frequencies and proportions, and symmetrically distributed continuous variables will be summarized by the mean and standard deviation (SD). Asymmetric variables will be presented as medians and interquartile ranges (IQR).

The table presents the baseline characteristics to be reported.

Number of participants	N=220
Age (years)	Mean ± (SD) or median (IQR)
Weight (kg)	Mean ± (SD)or median (IQR)
BMI at inclusion (kg/m^2)	Mean ± (SD) or median (IQR)
Gestational age at inclusion (weeks)	Mean ± (SD) or median (IQR)
Education level (1-3)	n/Total (%)

The number of babies (no.)	Mean ± (SD) or median (IQR)
Marital status (married or have partner/not)	n/Total (%)
Alcohol consumption before pregnancy (serving/week)	Mean ± (SD) or median (IQR)
Alcohol consumption during pregnancy (serving/week)	Mean ± (SD) or median (IQR)
Smoking status (current smoker)	n/Total (%)
Employed (yes/no)	n/Total (%)
Physical activity at work (active/sedentary)	n/Total (%)
Fertility treatment (no.)	n/Total (%)
Self-reported weekly physical activity level during pregnancy before inclusion (≤30 minutes or 30-60 minutes)	n/Total (%)
Minor health problems (no.)	n/Total (%)
Pelvic pain during pregnancy (yes/no)	n/Total (%)
Pelvic pain before pregnancy (yes/no)	n/Total (%)
Total cholesterol (mmol/L)	Mean ± (SD) or median (IQR)
HDL (mmol/L)	Mean ± (SD) or median (IQR)
LDL (mmol/L)	Mean ± (SD)or median (IQR)
HbAc1 (mmol/mol)	Mean ± (SD) or median (IQR)
Triglycerides (mmol/L)	Mean ± (SD)or median (IQR)
Steps per day (average steps/day)	Mean ± (SD) or median (IQR)
Active calories (calories/day)	Mean ± (SD) or median (IQR)
Moderate to vigorous physical activity (minutes/week)	Mean ± (SD) or median (IQR)
Active time (minutes/day)	Mean ± (SD) or median (IQR)
Floors walked (no./week)	Mean ± (SD) or median (IQR)
Minimum heart rate (beats/min)	Mean ± (SD) or median (IQR)
Average heart rate (beats/min)	Mean ± (SD) or median (IQR)
Maximum heart rate (beats/min)	Mean ± (SD)or median (IQR)
Resting heart rate (beats/min)	Mean ± (SD) or median (IQR)
Metabolic equivalent of task (MET/day)	Mean ± (SD) or median (IQR)
Move IQ (%type of physical activity)	Mean ± (SD) or median (IQR)

Section 6: Analysis

Outcome definitions

Primary outcome

The primary outcome, MVPA, is measured continuously (24/7) by an activity tracker and will be presented in minutes per week from randomization to GA week 28+6.

Secondary outcome

The secondary outcome is GWG, i.e. weight gained from the onset of the pregnancy to giving birth. GWG is determined as the difference between body weight on the day of birth and preconception body weight.

All other outcomes will not be presented with hypothesis testing, and they will be represented as exploratory outcomes.

Analysis methods

The treatment effects for the primary and secondary outcomes will be presented as mean differences between the treatment groups adjusted for physical activity at baseline. These values will be estimated from a multiple linear regression model. Analysis of the primary outcome based on multiple imputed datasets will be performed as a sensitivity analysis. The imputations will be performed using the R package "mice" [24]. 25 imputed data sets will be generated using the seed 24658. The imputations will be constructed on the following baseline covariates (body weight, age, group allocation, physical activity at baseline, socio-economic status). In addition, a sensitivity analysis will be performed to investigate whether the COVID-19 pandemic had an impact in the three study groups.

Missing data

The primary outcome will be measured by the activity tracker continuously (24/7) during the intervention. Possible missing data from the tracker due to not wearing the device or other reasons (e.g. skin rash) will be handled according to the predefined inclusion of the data in the analysis. For the primary outcome, a week will be 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 will be excluded and considered a missing day.

Additional analyses

Analyses describing associations between the level of physical activity, as measured by the activity tracker, and the secondary and exploratory outcomes in all three groups will be performed.

Harms

Information about adverse events (AEs) and serious adverse events (SAEs) will be registered and reported. The AEs/SAEs will be reported as frequency and percentage in the trial groups.

Statistical software

The statistical analysis will be performed using the latest version of R [24].

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