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Article

Comprehensive self-tracking of blood glucose and lifestyle with a mobile application in the treatment of gestational diabetes: a randomized controlled trial (eMOM GDM study)

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ABSTRACT

Introduction: Gestational diabetes (GDM) causes various adverse short-and long-term consequences for a mother and a child, and its incidence is increasing globally. So far, the most promising digital health interventions for GDM management have involved health care professionals to provide guidance and feedback. The principal aim of the study is to evaluate if comprehensive self-tracking could provide effective guidance for the self-management of GDM. We evaluate the effect of the eMOM GDM mobile application (app) on different maternal and neonatal outcomes. The follow-up of the study continues until 3 months postpartum.

Methods and analysis: This randomized controlled trial is carried out in Helsinki metropolitan area. We randomize 200 pregnant women with GDM into the intervention and the control group at gestational week (GW) 24-28 (baseline, BL). Participants in the intervention group use the eMOM GDM -app with continuous glucose meter (CGM) and activity bracelet for one week every month until delivery and an electronic 3-day food record every month until delivery. Data are collected by laboratory blood tests, clinical measurements, fingertip glucose measures, wearable sensors, air displacement plethysmography, and digital questionnaires. All participants receive regular antenatal care. The primary outcome is fasting plasma glucose change from BL to GW 35-37. Secondary outcomes include e.g., self-tracked fasting and postprandial glucose measured from fingertips, change in gestational weight gain, change in nutrition quality, change in physical activity, medication use due to GDM, birthweight, and fat percentage of the child.

Ethics and dissemination: The study has been approved by Ethics Committee of the Helsinki and Uusimaa Hospital District. The results will be presented in peer-reviewed journals and at conferences.

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Clinical trial registration: ClinicalTrials.gov identifier: NCT04714762

ARTICLE SUMMARY

Strengths and limitations of this study

- A mobile aid for self-management of GDM that combines lifestyle (e.g., nutrition, physical activity, and sleep) with continuous glucose levels in a single app.
- Multiple aspects of maternal outcomes and neonatal outcomes are compared between the intervention and the control group.
- Usage logs enable investigations of the effect of compliance with the eMOM GDM app on the maternal and neonatal outcomes. However, we can't fully isolate or mitigate the effect of sensors' own apps for supporting management of GDM.
- Although not clinically evaluated here, the eMOM GDM service has its own user interface for health care professionals, which shows self-tracking data from the patients online. This enables future remote controlling and guidance of women with GDM.
- **Keywords:** gestational diabetes, GDM, mobile application, app, self-tracking, wearable sensors, continuous glucose meter, activity bracelet, food diary.

INTRODUCTION

Digital health holds a promise for more efficient and improved health care with minor additional human resources. Gestational diabetes (GDM) is a type of diabetes that develops during pregnancy[1]. Today the burden of GDM on health care system and economy is remarkable since the incidence of GDM is increasing together with obesity globally [2], and it is associated with a range of adverse short- and long-term consequences for both a mother and a child [3–7]. The different digital health interventions have also been tested in women

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with GDM and a recent meta-analysis shows that interventions where participants receive weekly or more frequent feedback from health care personnel have shown the potential to improve glycemic control [8]. However, mobile app interventions without such substantial input from health care professionals are limited and lack effectiveness [9–11]. The recent app intervention study by Yew et al. [12] found improvements in mean glucose and in proportion of off-target preprandial and 2-h postprandial measurements. However, their app included a chat feature with health care team, which use and effect on the results remained unclear. In this study, we evaluate if the effectiveness can be increased with eMOM GDM mobile app which visualizes continuous glucose data together with lifestyle data in a single view without additional communication with health care personnel. Comprehensive self-tracking has been identified as a desirable feature for increasing competence to self-manage GDM but it has not been clinically evaluated before [13].

METHODS

Study design

Participants are randomized 1:1 into the intervention and the control group. Participants in the intervention group are instructed to use the eMOM GDM app with continuous glucose meter (CGM) and activity bracelet one week/month until delivery. During the same week when participants have the CGM installed, participants are instructed to keep an electronic food diary for 3 days. After keeping the food diary, the nutrition entries are checked and corrected in a call by a nutritionist. In addition to this instructed use, participants can use the eMOM GDM app with activity bracelet and food-tracker freely.

Both groups will receive standard care (please see *Standard care for both groups)*. Participants are invited to the follow-up study at 3 months postpartum. We follow the SPIRIT checklist [14] in the study design and reporting. Study design and data collection is depicted

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in figure 1, please see details for laboratory tests, measurements, and questionnaires in Section *Measurements*.

figure 1. Design of the randomized controlled trial.

Participants

Inclusion and exclusion criteria are given in Table 1. Women with GDM are randomized into the intervention and the control group using stratification at GW 24-28. Strata are gestational week (GW) of GDM diagnose (early: < 24 GW or late: 24-28 GW), parity (primiparous or multiparous) and Body Mass Index (BMI) (< or ≥ 30 kg/m^2). Three strata resulted in eight blocks. The Finnish Current Care Guidelines provide the thresholds for diagnosing GDM based on 2-hour 75g oral glucose tolerance test (OGTT): 0 h ≥ 5.3 mmol/l, 1 h ≥ 10.0 mmol/l and 2 h ≥ 8.6 mmol/l [15]. Participants are voluntary and they are allowed to withdraw any point without any reason, and they have right to cancel the consent. This means that all the research data collected in the study, which are not processed as research results, will be deleted. If medication is started, the participant will drop out from the study and the data collected until the decision to start medication will be collected unless the participant wishes otherwise.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria:	Exclusion criteria:
• 18 to 45 years • GDM diagnosis at GW 24-28	• type 1 or type 2 diabetes • use of medication that influences glucose metabolism (such as continuous therapy with oral corticosteroids or metformin), • physical disability • current substance abuse • severe psychiatric disorder (that complicates participation to the study) • significant difficulty in cooperating (e.g., inadequate Finnish language skills).

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Recruitment and consent

Participants are recruited from antenatal clinics from the Helsinki metropolitan area at GW 24-28. Local nurses at the municipal maternal clinics in Helsinki, Espoo and Vantaa inform about the possibility to participate in the eMOM GDM study in peer-support groups and share flyers in one-to-one meetings. We started the recruitment in 3/2021 and we plan to continue until 01/2023. Women who agree to participate sign two consent forms, one copy for themselves and one for the study nurse.

Blinding

For each block (see Section *Participants*), envelopes consisting of equal number of intervention and control cases were created for blinding. Based on the participant's status, a study nurse opens a sealed envelope from the respective block. The content of the envelope determines whether the participant is assigned to the intervention or to the control group. This approach balances the allocation of subgroups of participants to intervention and control groups in a blinded manner.

Description of eMOM GDM app and its wearable sensors

The eMOM GDM app and its integration to the medical personnel user interface (UI) was developed in 2020. The eMOM GDM app visualizes lifestyle data (physical activity, sleep, and nutrition) together with tissue glucose data in a single view (see figure 2A and figure 2B). For displaying the data, eMOM GDM app has two views, a week view (see figure 2A) and a day view (see figure 2B). The information from the sensors and food tracker is updated each 10 min to the eMOM GDM app. We included an information section regarding pregnancy and GDM (see figure 2C). Based on a recent literature-review [13] providing reliable information about how to manage GDM (particularly what to eat and how the fetus is developing) should be integrated in the GDM apps, so that no separate app for this is needed.

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Medtronic Guardian Connect CGM with Enlite sensor (Medtronic, Dublin, Ireland; see figure 3) continuously measures tissue glucose. Flexible filament is inserted just under the skin to measure glucose levels in interstitial fluid approximately every 5 minutes. eMOM GDM app shows these detailed glucose values when tapping the glucose curve on the screen (see figure 2D). Glucose values are sent to the mobile phone via Bluetooth. Medtronic requires calibration of the sensor by fingertips blood glucose measurements 2 times a day.

Garmin Vivosmart 3 (Garmin International, KA, USA; see figure 3) is a wrist-worn optical heart rate and activity tracker which measures activity, sleep, and heart rate continuously based on its optical heart rate sensor, and 3D acceleration. Garmin Vivosmart 3 has been found to be feasible amongst pregnant women with good ratings on user experience [16] and measures steps well at slow walking speeds [17]. The tracked parameters include steps, estimated energy expenditure in calories (based on motion and heart rate), stairs, walking and running distance, all-day heart rate and stress. It connects automatically to a mobile app (Garmin Connect) and data is stored automatically to the cloud, where it can be accessed via application programming interfaces (APIs).

A dedicated food-tracker was developed by Helsinki University Hospital to make the food intake data collection easier for pregnant women. A user enters the time of each meal, food items consumed and portion sizes to the food-tracker. The food-tracker fetches the food items and their nutrient contents from Fineli food composition database[1], calculates nutrient intake and shows the amounts of the energy yielding nutrients and fiber to the user. This data is transferred to eMOM GDM app where the energy intake from each energy yielding nutrient is visualized as stacked bars (see figure 2B). More detailed information (recorded food items,

[1] Finnish National Institute for Health and Welfare, http://www.fineli.fi

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nutrient intake in grams) can be accessed (see figure 2E) by tapping the stacked bar (see figure 2B).

figure 2. Screenshots of main views in eMOM app. A) a week view for self-tracking data (Copyright: Fujitsu Finland), B) a day view for self-tracking data (Copyright: Fujitsu Finland), C) pregnancy and GDM related information (Copyright: Helsinki University Hospital), D) detailed glucose view (Copyright: Fujitsu Finland), and E) detailed nutrition view (Copyright: Fujitsu Finland).

Standard care for both groups

All participants in the study receive standard care, in addition to the study protocol. The public health care system in Finland offers all pregnant women antenatal health care on a regular basis in municipal maternity clinics at primary health care centers. A doctor and a nurse are following the pregnancy in collaboration. Sessions are divided into periodic audits (basic visits) and discretionary additional visits. The periodic health check includes a minimum number (9-10) of visits with a nurse, and two doctor examinations designed for normal, low risk pregnancies. The first medical check-up is during GW 8-10. Maternity clinics and hospitals have provided detailed instructions on when the mother should be sent to the hospital for further examinations and follow-up [18].

A 2h-OGTT is performed normally at GW 24-28, but if the risk of the GDM is considered high (BMI >35kg/m^2, previous GDM, glycosuria in early pregnancy, incidence of type 2 diabetes in grandparents, parents or siblings, oral corticosteroid therapy, polycystic ovary syndrome), OGTT is performed already at GW 12-16. After a GDM diagnosis, the women receive guidance on diet, physical activity and self-monitoring of blood glucose with electronic fingertip glucose meters [15]. In case of repeated fasting capillary glucose of ≥5.5

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mmol/l or a one-hour postprandial value of ≥7.8 mmol/l, the maternity clinic refer the woman to a maternity hospital for further assessment regarding need of medication [15].

Objectives and hypotheses

The principal aim of the study is to evaluate the effectiveness of the eMOM GDM application on maternal and neonatal outcomes by comparing intervention and control groups. The follow-up of the study continues until 3 months postpartum. The specific objectives of the intervention study are to compare between the intervention and the control groups:

1. Differences in maternal glucose levels during pregnancy,
2. differences in physical activity levels during pregnancy,
3. differences in total diet during pregnancy,
4. difference in the need for medication due to GDM,
5. difference in gestational weight gain (GWG),
6. birthweight, incidence Large-for-Gestational-Age (LGA) and macrosomic (birthweight >4000g) newborns, and infant's body composition,
7. differences in motivation during the pregnancy, and
8. differences in physical activity, total diet, weight retention and glucose values 3 months postpartum.

Main hypothesis: Fasting plasma glucose, between baseline (BL) and GW 35-37, will decrease more in the intervention than in the control group.

Outcomes

Primary outcome is the change in fasting plasma (fP)-glucose from BL (GW 24-28) to GW 35-37. The main secondary outcomes are given in Table 2.

Table 2. The main secondary outcomes.

The main secondary outcomes
1. Difference in fingertips fasting and postprandial glucose values during pregnancy,

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2. difference in fingertip glucose area under the curve (AUC) during pregnancy,
3. change in Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) during pregnancy and 3 months postpartum,
4. difference in physical activity level during pregnancy and 3 months postpartum,
5. difference in total diet during pregnancy and 3 months postpartum,
6. difference in medication use due to GDM (insulin, metformin),
7. difference in GWG and postpartum weight retention,
8. difference in birthweight (SD) of child,
9. difference in LGA of child and macrosomia,
10. difference in infant's body composition,
11. difference in neonatal hypoglycemia incidence within a week from birth,
12. difference in motivation to manage GDM during pregnancy, and
13. difference in fP-glucose and 2-hour blood glucose levels measured with OGTT (75g) at 3 months postpartum.

Measurements

We take measurements with multiple techniques and sensors. All the measurements, except measurements specific to eMOM GDM app intervention are taken from both groups (see a summary in Table 3).

Table 3. Measurements for intervention and control groups:

Measurements for intervention and control groups:	**Baseline GW 24-28**	**III trim GW 35-37**	**Birth**	**Postpartum (3 months)**
○ Background questionnaire	•			
○ OGTT	•			•
○ Fingertip glucose measurements	•	•		
○ Laboratory blood samples	•	•		•
○ Questionnaires*	•	•		•
○ Physical activity (UKK RM42 - accelerometer)	•	•		•
○ Heart rate variability (Firstbeat Bodyguard 2) (analyses shown to participants only after postpartum visit)	•	•		•
○ Cord blood			•	
○ Placental weight			•	
○ Infant's anthropometry (Pea Pod)			•	
Measurements only for intervention group:				
○ Data from sensors and apps: eMOM GDM app, Garmin Vivosmart, Medtronic CGM, food tracker ○ Technology acceptance questionnaire (UTAUT-technology)	1 app week + 3 normal care weeks repeatedly until delivery			
○ Usability questionnaire	•			
○ Semi-structured interview**		•		

* *Questionnaires*= Food frequency questionnaire (FFQ), depression, motivation, and quality

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of life. At the postpartum study visit (3 months) FFQ and depression questionnaire.
** 20 participants will conduct the semi-structured interview about the user experience with eMOM GDM app

Background information

Age, BMI, parity and previous GDM status are collected from hospital registries, and socioeconomic status (e.g., education, occupation), alcohol use, possible special diet, and experience with self-tracking from a background questionnaire.

Maternal glucose levels

Maternal glucose levels are collected in the intervention and the control groups with 2h-OGTT at GW 12-16 (early) or GW 24-28 (late) as well as 3 months postpartum, with fingertip glucose measures (e.g. fasting glucose, postprandial glucose, AUC) (Contour Next One, Ascensia Diabetes Care, Basel, Switzerland) from BL until delivery and with laboratory blood samples (fP-glucose, HbA1c, fP-insulin) at study visits at BL, GW 35-37, and 3 months postpartum, and additionally in the intervention group with a CGM (Medtronic Guardian Connect) 1 week/month from BL to delivery.

Maternal physical activity

Maternal physical activity is extracted from both groups at BL, GW 35-37, and 3 months postpartum with two "blind" sensors: UKK RM 42 and Firstbeat Bodyguard 2 (see figure 2). Movement is measured with UKK RM42 (UKK Institute, Tampere, Finland). It is a triaxial accelerometer that measures the device movement located either at the hip during waking hours and at the wrist during the time in bed for sleeping (see Sensor 4 in figure 3). The data analysis is based on validated MAD-APE algorithms [19,20]. The amount of daily physical activity is described in durations and intensity in METs, the amount of sedentary behavior (lying, sitting, and standing) in durations, and sleep as movement categories. These analyses have been employed in population-based studies of Finnish adults [21,22].

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Heart rate variability (HRV) is measured with Firstbeat Bodyguard 2 sensor (Firstbeat Technologies, Jyväskylä, Finland) which is a chest worn wearable device which measures beat-to-beat heart rate variability and activity (3D acceleration) continuously for three days. The device is attached to the chest with two disposable clinical grade ECG electrodes (see Sensor 1 in figure 3). The device is able to continuously measure beat-to-beat heart rate variability with <3ms error and >99.9% detection rate as compared to clinical grade ECG [23]. Proprietary analytics software (Firstbeat Lifestyle Assessment, Firstbeat Technologies, Jyväskylä, Finland) is used to transform the recorded beat-to-beat and motion data into continuous assessment of energy expenditure, VO_2, physical activity, stress, and recovery. The methods has been validated widely and in several studies including [24,25].

Physical activity measures are also collected in the intervention group with activity bracelet Garmin Vivosmart 3 one week/month from BL until delivery (see Sensor 3 in figure 3 and Section *Description of eMOM GDM app and its wearable sensors*).

figure 3. The sensors used in the study. The sensors on the left (1. HRV sensor and 4. Movement sensor) are worn by both control and intervention group. The Movement sensor is a small box, which is attached either to a belt or to a bracelet. Sensors on the right (2. CGM and 3. Activity bracelet) are part of the intervention.

Maternal nutrition

We measure maternal total diet including food consumption and nutrient intake among intervention and control women during the preceding month with a digital semiquantitative 142-item food-frequency-questionnaire (FFQ) (updated from [26]) at BL, GW 35-37, and 3 months postpartum. FFQ is used for intervention effect estimation. Nutritional outcomes include e.g., intake of fruits and vegetables, wholegrain cereals, sugar, protein, carbohydrates, fiber, unsaturated and saturated fat, vitamins, and minerals.

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Maternal gestational weight gain and weight retention 3 months postpartum

Weights (in kg) are extracted from the maternity card and at study visits at BL and GW 35-37, within 2 days after birth, and 3 months postpartum.

Neonatal outcomes

Neonatal anthropometric measures at birth are extracted from hospital registry; birthweight (SD), birth length, incidence of LGA/macrosomic newborn (>+2SD / >4000g), and newborn body composition (body fat%, lean body mass%) by Pea Pod (COSMED, Italy, Rome) air-displacement plethysmography [27–29] within 2 days after birth. Also, Apgar scores, transfer to intensive care and intravenous glucose infusion of newborn are collected.

Psychological factors, motivation, and health-related quality of life

Maternal depression and health-related quality of life are collected with the digital questionnaires at BL, GW 35-37, and 3 months postpartum. Motivation is collected with the digital questionnaires at BL and GW 35-37. Depression is measured with Edinburgh depression postnatal depression scale (EPDS) [30], which is also used during pregnancy (e.g., [31]), health-related quality of life with 15D questionnaire [32], and motivation with Treatment Self-Regulation Questionnaire (TSRQ) [33] and Perceived Competence for Diabetes Scale (PCDS) [33]. The digital questionnaire data is collected through Qualtrics[2] (Qualtrics International Inc., Seattle, United States).

Measures about the intervention

We measure the app usage by logging the time and type of every interaction with the eMOM GDM app. Human factors relating to app use are measured with Unified Theory of Acceptance and Use of Technology (UTAUT) questionnaire [34], Software Usability

[2] www.qualtrics.com

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Measurement Inventory (SUMI) [35], and with a semi-structured interview on user experience with the eMOM GDM app with randomly selected twenty participants.

Data analysis

We will analyze the data using RStudio (Version 1.1.456, RStudio, Boston, USA) and perform the analyses according to intention-to-treat principle. Missing data will not be replaced. For comparing maternal outcomes and neonatal outcomes between intervention and control group we will use classical statistical tests (such as t-test, χ^2-test, and ANCOVA) depending on type of the variable and its distribution (i.e., normality and homogeneity). The comparisons of changes between the control and the intervention group will be performed using either ANOVA of change from baseline or ANCOVA ~~models (if assumptions of normality and homogeneity are met)~~, having the BL measurements as covariate [36]. The selection depends on the possible differences at baseline [36]. ~~-~~Other maternal covariates will be maternal socioeconomic situation (education, occupation), age at childbirth, BMI, parity, and smoking during pregnancy. The birthweights will be adjusted according to [37]. Regarding the eMOM GDM app use, we will investigate correlations between usage patterns of eMOM GDM app and outcomes (maternal and neonatal). We will conduct a cluster analysis for the usage patterns to identify effective usage strategies of eMOM GDM app similar to apps designed for type 2 diabetes management [38].

For the CGM data, we will conduct time series analysis using standard techniques [39], such as *area under the curve* [40,41] and *mean amplitude of glycemic excursions* [42]. Interim data analysis will be performed by data analysis team (MK, LM, and PM) when the research data from a half of the participants (N=100) is being collected. Study nurses will remain blinded to the interim results, and we will blind the statistical analyses by asking an external person to recode the participants before conducting final analyses. The final dataset is

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accessed by data analysis team (MK, LM, and PM). The final decision to terminate the trial will be made by the principal investigator (SK).

Sample size

To detect at least a 0.32 mmol/l between-group mean difference in the fP-glucose (primary outcome) response to the intervention ($\alpha<0.05$, power=95%, an assumed dropout rate of 40%), a sample of 200 women (100 in each intervention arm) is needed for the intervention study. This anticipated difference of 0.32 mmol/l between the intervention group and control group corresponds to 0.7 SD of variation in fP-glucose change observed previously in similar women and stage of pregnancy (SD needed for power calculation has been calculated from the Finnish Gestational Diabetes Prevention Study -population; SD for change in fP-glucose value between II and III trimesters in women who got GDM diagnoses at II trimester) [43].

eMOM GDM system implementation and data maintenance

The system implementation was designed to support wider employment of eMOM GDM service concept as a part of future digital health care path for women with GDM in Helsinki metropolitan area. Technical implementation of the eMOM GDM app as well as browser-based UI for health care professionals were conducted by Fujitsu Finland Oy. The data transfer to the eMOM GDM app and professional UI is implemented in the cloud so that eMOM app's back-end server fetches data from a data integration server. Data integration server (implemented by Elisa Corp.) gathers data from sensors' and food tracker's cloud services. The data from eMOM GDM service's back-end server is further transferred to secure HUS Data Lake environment (Microsoft HDInsight Hadoop cluster).

Feasibility study

Before this RCT trial, we conducted feasibility studies of eMOM GDM app, wearable sensors and food-tracker involving women with GDM (data not published yet). The digital

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food-tracker used in this study was originally speech-enabled, but in the feasibility study we noticed that a large majority of participants preferred typing over speech. Thus, we discontinued the support for speech recognition.

Ethics and dissemination

The eMOM GDM study is in accordance with the Declaration of Helsinki[3]. All the participants sign informed consent forms, and they are instructed that they can withdraw at any point during the study. Data during any processes or analyses is pseudonymized, and it does not contain personal information that could be directly linked to any individual. For example, a participant of the intervention group gets a pseudonym (ID based) email address, which the participant uses when she logs to eMOM GDM app and the sensor-associated apps. We have ethical approval from ethical committee of HUS, and study permissions from three cities (Helsinki, Espoo, and Vantaa) in the Helsinki Metropolitan area to recruit participants.

As a part of quality assurance, the study is being monitored by an external institution, Helsinki University Central Hospital's Study Monitor of Clinical Research Institute[4], according to legislation, official guidance, and good clinical practice (GCP)[5]. The auditing visits are conducted every 6 months during the trial, and the auditing process is independent from investigators and the sponsor.

Important protocol modifications will be communicated with research group, Ethical committee of Helsinki University Hospital, and ClinicalTrials.gov.

Sponsor provides facilities for the trial and funder partly funds the trial, but they do not have role in study design. There are monthly technical steering group meetings by project partners,

[3] www.wma.net
[4] https://hyksinstituutti.fi/clinical-research-institute-huch/?lang=en
[5] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice

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in which the progress of the trial is followed. However, the ultimate authority to make decisions regarding the clinical trial is principal investigator (SK).

The results of the eMOM GDM study will be published in peer-reviewed journals and at national and international scientific conferences. We promote open science by blogs and interact actively with the media, including social media (e.g., Twitter and LinkedIn), to gain visibility to our findings among journalists and among non-research community as well.

Patient and Public Involvement Statement

Both women with GDM and registered nurses from the Helsinki Metropolitan Area were involved in the design process of the eMOM GDM service concept. Based on the feedback from the use of the first version of the eMOM GDM app, it was modified into version which is used in the eMOM GDM clinical trial. The user-centered design process involved women with GDM (N=21) who did not participate in the clinical trial and the results will be published in a separate article. The local nurses gave insights into the design of the professional UI. Additionally, the Helsinki Metropolitan Area nurses were involved in the recruitment of women with GDM for this clinical trial (see Section *Recruitment and Consent*).

Adverse events

All participants will be under standard care, and thus will be in close medical observation. In the case of adverse or harmful events, study nurses will report to principal investigator (SK) and the appropriate response to these will be discussed within the research group. All participants are insured with the patient injury insurance by Helsinki University Hospital.

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DISCUSSION

Our approach differentiates from existing GDM app interventions in three main aspects. First, we have wearable sensors integrated with the eMOM GDM app. This enables viewing self-tracking data in one place. Objectively and automatically measured, and constantly available data through wearable sensors data can be expected to support learning. However, learning through self-tracking requires active agency from women with GDM, as associations between lifestyle and nutrition are complex and difficult to identify, especially within first weeks after the GDM diagnosis [44]. Thus, it remains to be seen if this type of feedback, being quite different from what women with GDM receive in standard care, is effective enough for improving maternal glycemic levels and neonatal outcomes. Secondly, our intervention differentiates from other app-based interventions in timewise. Our intervention has clearly defined instructions when participants should use the app (one week per month) and keep food diary (3 days per month). These time periods were chosen based on the validity (3-day food diary have shown to provide equally valid results with 9-day food diary [45]), decrease of engagement with mHealth over time [46], practicality (battery of CGM lasts approx. a week), and costs (the price of the sensors; we were able to rotate them amongst participants). The effects of this type of periodical intervention remain unclear, and we will collect experiences on this with interviews with the participants. Thirdly, the system does not consist of an app only, as there is UI for professionals to view the data from the CGM, activity bracelet and food diary from each participant in the intervention group. In this study, the professional UI is used only for remote monitoring of the technical data flow from the participants. In the future, the professional UI is planned to be used as a resource for monitoring and giving guidance for women with GDM. Together with the eMOM GDM app, the professional UI forms a novel service concept, which can be employed as future digital health care path for women with GDM.

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The comprehensive self-tracking approach also poses challenges. As we are utilizing multiple sensors and they have their own apps, it is difficult to identify how much the eMOM GDM app and other apps (CGM's app and activity bracelet's app) influence the learning. Especially, the CGM solely has been identified to facilitate self-discovery, i.e., finding associations between lifestyle (e.g., nutrition) and glucose levels [47,48]. In order to evaluate the eMOM GDM app's role, we will log the interactions with the app, and we will interview a subgroup of participants about the user experience with the app. By doing so, we are able to evaluate the compliance and engagement with the app, which has been identified as a shortcoming in studies evaluating the effectiveness of GDM apps [49]. The other challenges emerge from technical implementation and maintenance. The sensors' apps need to be installed in compatible mobile phones and the data is fetched to eMOM GDM app through APIs in the cloud services. This requires active monitoring for the updates regarding compatibility issues between phones and sensors and their APIs.

Contributors

SK, SH, MK, PM, GJ planned the design of the study. MK, LM, PM, and SK planned the analysis of the data and performed the power calculation. SN, SMV, TEK were responsible of methods of dietary data collection and calculations. HS, HV-Y, and IK designed the collection of physical activity data. MK and SK wrote the draft and all authors MK, SK, LM, PM, GJ, SN, SMV, HS, HV-Y, IK, TEK, SH have reviewed and approved the final manuscript.

Conflicts of interests

IK is a shareholder of Firstbeat Technologies and products of Firstbeat Technologies are used in the present study. These are sold on commercial basis to researchers. Firstbeat does not fund or supervise the study as an organization

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Funding

This work was supported by Business Finland grant number 860/31/2018 (eMOM GDM).

Data sharing statement

This protocol is available for the public.

Ethics Approval

The Ethics Committee of the Helsinki and Uusimaa Hospital District has accepted the study protocol (HUS-2165-2018-3).

Acknowledgments

We gratefully acknowledge the contribution of Fujitsu Finland Oy for the technical implementation of eMOM app and Elisa for sensor integration. We wish to thank all the women with GDM in Finland taking part in the research so far, and the study nurses Jaana Palukka, Sanna Lampi and Milla Tuhkanen.

Provenance and peer review

Not commissioned; externally peer reviewed.

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Protocol date

May 27, 2022

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Sponsor

Helsinki University Hospital

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figure 1. Design of the randomized controlled trial.

figure 2. Screenshots of main views in eMOM app. A) a week view for self-tracking data (Copyright: Fujitsu Finland), B) a day view for self-tracking data (Copyright: Fujitsu Finland), C) pregnancy and GDM related information (Copyright: Helsinki University Hospital), D) detailed glucose view (Copyright: Fujitsu Finland), and E) detailed nutrition view (Copyright: Fujitsu Finland).

figure 3. The sensors used in the study. The sensors on the left (1. HRV sensor and 4. Movement sensor) are worn by both control and intervention group. The Movement sensor is

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a small box, which is attached either to a belt or to a bracelet. Sensors on the right (2. CGM and 3. Activity bracelet) are part of the intervention.

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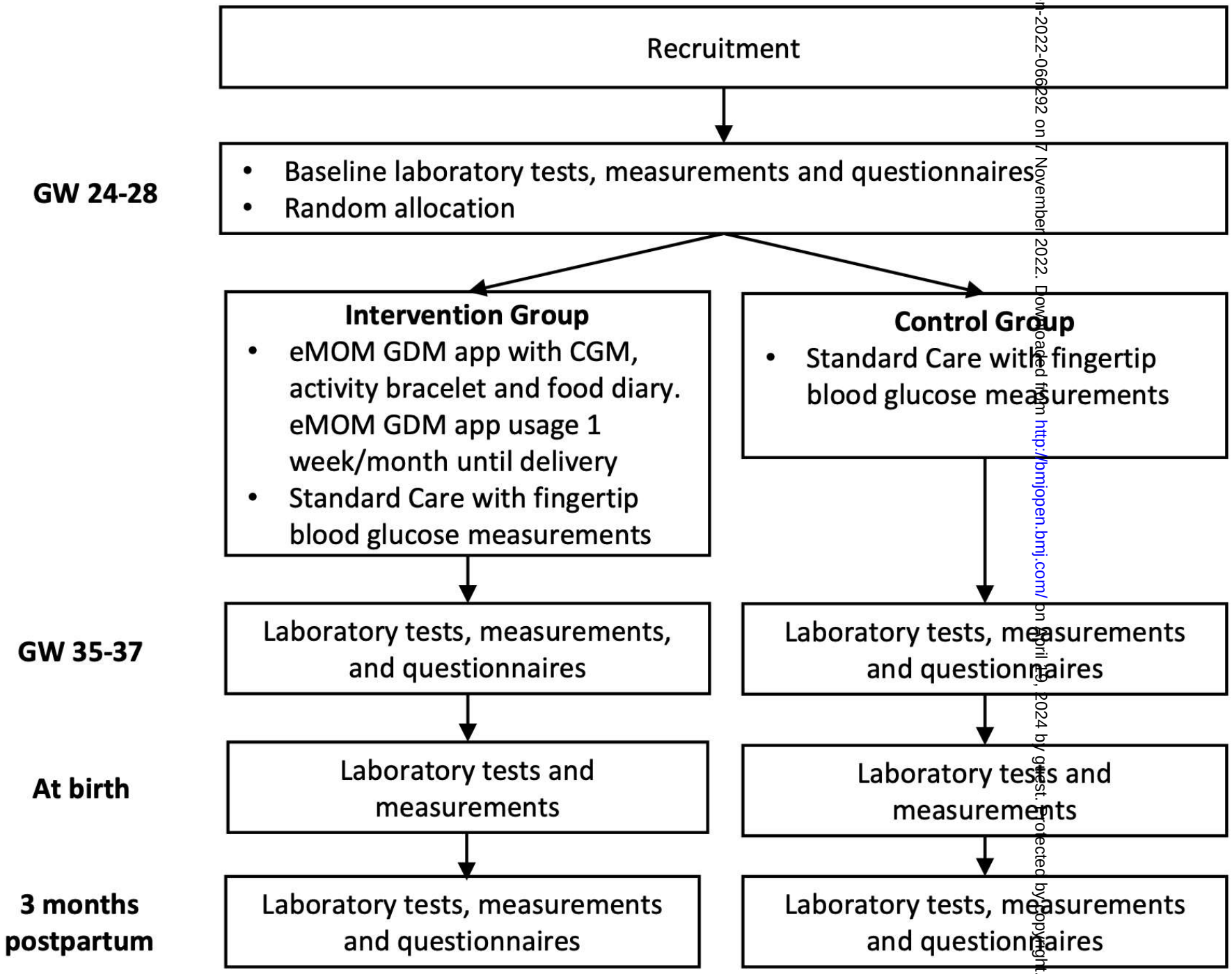

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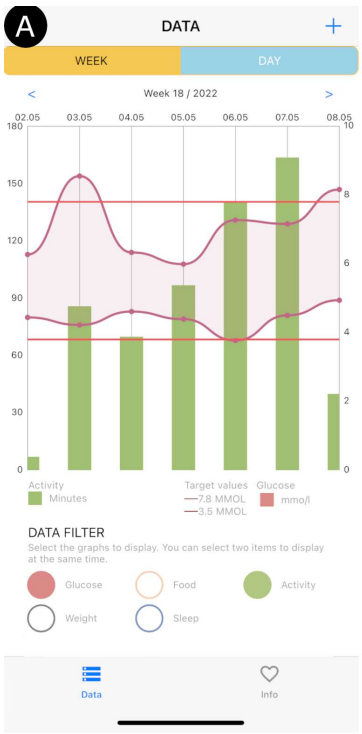

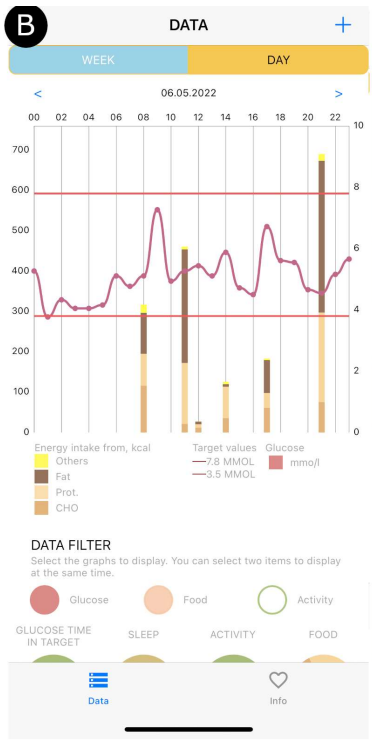

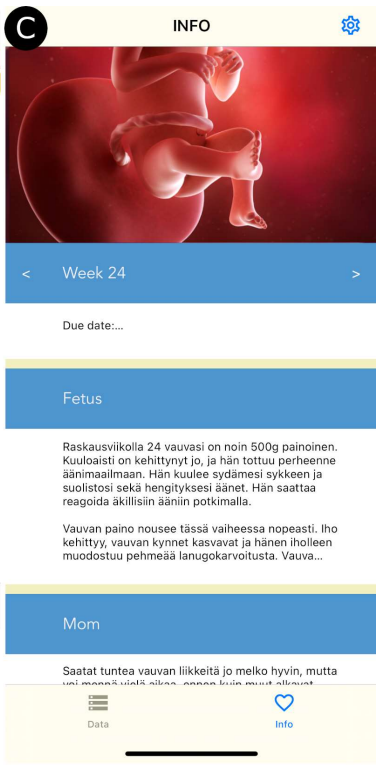

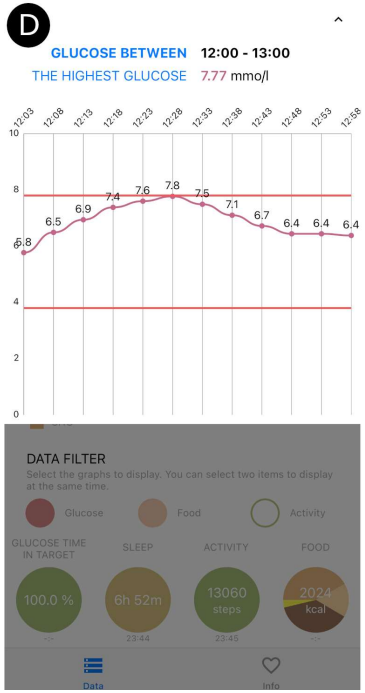

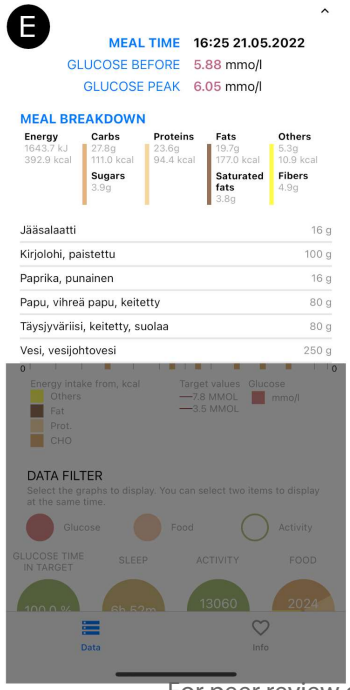

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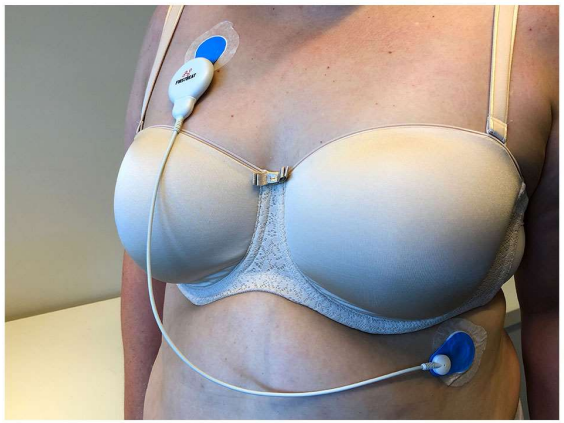

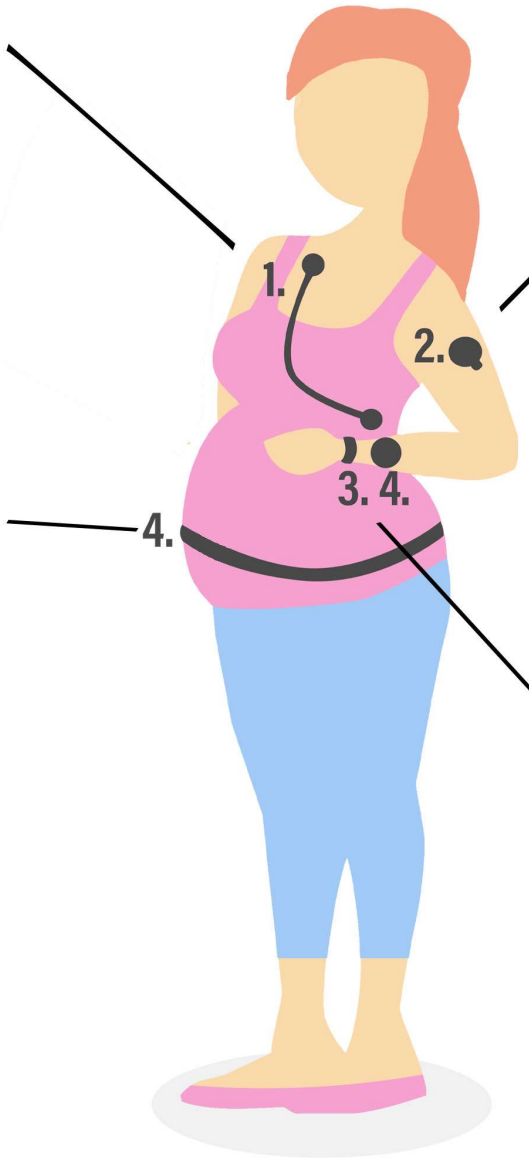

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	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	3

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		registered, name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	20
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,19
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	20
Roles and responsibilities: sponsor and funder	#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	16
Roles and responsibilities: committees	#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,	16

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		if applicable (see Item 21a for data monitoring committee)	
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	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	8-9
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, non-inferiority, exploratory)	4
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

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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: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
Interventions: modifications	#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)	5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
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	9

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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)	see figure 1
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	14
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	#16b	Mechanism of implementing the allocation	6

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concealment mechanism		sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A, Data will be blinded to data analysts and there is no need to reveal the allocation for the analysis.
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related	9-13

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		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	
Data collection plan: retention	#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	5
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	14-15
Statistics: outcomes	#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	13-14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis	#20c	Definition of analysis population relating to protocol	13

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population and missing data		non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring: formal committee	#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	15-16
Data monitoring: interim analysis	#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	14
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	17
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16-17
Ethics and dissemination			

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Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	3
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)	16
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A, not applicable.
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14-15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14

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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	17
Dissemination policy: trial results	#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	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A, we have no authorship eligibility guidelines and we don't intend to use professional writers.
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Available, but in Finnish. Added on

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			request.
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	N/A, we have no such intentions.

None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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Comprehensive self-tracking of blood glucose and lifestyle with a mobile application in the management of gestational diabetes: a study protocol for a randomized controlled trial (eMOM GDM study)

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Article

Comprehensive self-tracking of blood glucose and lifestyle with a mobile application in the management of gestational diabetes: a study protocol for a randomized controlled trial (eMOM GDM study)

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ABSTRACT

Introduction: Gestational diabetes (GDM) causes various adverse short-and long-term consequences for a mother and a child, and its incidence is increasing globally. So far, the most promising digital health interventions for GDM management have involved health care professionals to provide guidance and feedback. The principal aim of this study is to evaluate the effects of comprehensive and real-time self-tracking with eMOM GDM mobile application (app) on glucose levels in women with GDM, and more broadly, on different other maternal and neonatal outcomes.

Methods and analysis: This randomized controlled trial is carried out in Helsinki metropolitan area. We randomize 200 pregnant women with GDM into the intervention and the control group at gestational week (GW) 24-28 (baseline, BL). The intervention group receives standard antenatal care and the eMOM GDM app, while the control group will receive only standard care. Participants in the intervention group use the eMOM GDM -app with continuous glucose meter (CGM) and activity bracelet for one week every month until delivery and an electronic 3-day food record every month until delivery. The follow-up visit after intervention takes place 3 months postpartum for both groups. Data are collected by laboratory blood tests, clinical measurements, capillary glucose measures, wearable sensors, air displacement plethysmography, and digital questionnaires. The primary outcome is fasting plasma glucose change from BL to GW 35-37. Secondary outcomes include e.g., self-tracked capillary fasting and postprandial glucose measures, change in gestational weight gain, change in nutrition quality, change in physical activity, medication use due to GDM, birthweight, and fat percentage of the child.

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Ethics and dissemination: The study has been approved by Ethics Committee of the Helsinki and Uusimaa Hospital District. The results will be presented in peer-reviewed journals and at conferences.

Clinical trial registration: ClinicalTrials.gov identifier: NCT04714762

ARTICLE SUMMARY

Strengths and limitations of this study

- A mobile app for self-management of GDM that combines lifestyle (e.g., nutrition, physical activity, and sleep) with continuous glucose levels in a real time and without support from health care personnel is evaluated in randomized controlled trial.
- Maternal outcomes and neonatal outcomes are compared between the intervention and the control group with different measurements, including physical activity sensors and neonatal air displacement plethysmography.
- Usage logs enable investigations of the effect of compliance with the eMOM GDM app on the outcomes.
- As a limitation, we can't fully isolate or mitigate the effect of sensors' own apps on the outcomes.
- **Keywords:** gestational diabetes, GDM, mobile application, app, self-tracking, wearable sensors, continuous glucose meter, activity bracelet, food diary.

INTRODUCTION

Digital health holds a promise for more efficient and improved health care with minor additional human resources. Gestational diabetes (GDM) is a type of diabetes that develops during pregnancy [1]. Today the burden of GDM on health care system and economy is remarkable since the incidence of GDM is increasing together with obesity globally [2], and

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it is associated with a range of adverse short- and long-term consequences for both a mother and a child [3–7]. The primary treatment for GDM and glycemic control is through adjustments toward heathier lifestyle, especially changing the diet and increasing exercising [8,9]. It is critical that women with GDM are supported in this behavior change [10]. The lifestyle interventions for the treatment of women with GDM have been shown to reduce the incidence of large-for-gestational-age (LGA) [8,11] and postpartum weight retention [12]. For this support different digital health interventions have been tested in women with GDM and a recent meta-analysis shows that interventions where participants receive weekly or more frequent guidance and feedback from health care personnel have shown the potential to improve glycemic control [13]. For example, in a study by Miremberg et al. [14] women with GDM received dietary tips for optimizing off-target measurements and reassuring and positive messages every evening via e-mail. However, mobile app interventions without such substantial input from health care professionals are limited and lack effectiveness [15–17]. Recently, Yew et al. [18] found improvements in mean glucose and in proportion of off-target preprandial and 2-h postprandial measurements. However, their app included a chat feature with health care team, which use and effect on the results remained unclear [19]. In this study, we evaluate if the effectiveness can be increased with the eMOM GDM mobile app which visualizes continuous glucose data together with lifestyle data in a single view in a real time without involvement of health care personnel. Comprehensive self-tracking with wearable sensors has been identified as a desirable feature for increasing competence to self-manage GDM [20,21], but has not been clinically evaluated before.

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METHODS

Study design

Participants are randomized 1:1 into the intervention and the control group. The intervention group receives standard antenatal care and the eMOM GDM app, while the control group will receive only standard care. Participants in the intervention group are instructed to use the eMOM GDM app with continuous glucose meter (CGM) and activity bracelet one week/month until delivery. During the same week when participants have the CGM installed, participants are instructed to keep an electronic food diary for 3 days. After keeping the food diary, the nutrition entries are checked and corrected in a call by a nutritionist. In addition to this instructed use, participants can use the eMOM GDM app with activity bracelet and food-tracker freely. Participants in both groups are invited to the follow-up visit at 3 months postpartum.

We follow the SPIRIT checklist [22] in the study design and reporting. Study design and data collection is depicted in figure 1, please see details for laboratory tests, measurements, and questionnaires in Section *Measurements*.

figure 1. Design of the randomized controlled trial.

Participants

Inclusion and exclusion criteria are given in Table 1. Women with GDM are randomized into the intervention and the control group using stratification at GW 24-28. Strata are gestational week (GW) of GDM diagnose (early: < 24 GW or late: 24-28 GW), parity (primiparous or multiparous) and Body Mass Index (BMI) (< or ≥ 30 kg/m^2). Three strata resulted in eight blocks. The Finnish Current Care Guidelines provide the thresholds for diagnosing GDM based on 2-hour 75g oral glucose tolerance test (OGTT): 0 h ≥ 5.3 mmol/l, 1 h ≥ 10.0 mmol/l

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and 2 h ≥ 8.6 mmol/l [23]. Participants are voluntary and they are allowed to withdraw any point without any reason, and they have also right to cancel the consent. If a participant withdraws, the research data collected in the study will stored and included in the analysis. If a participant cancels the consent, all the data which are not processed as research results, will be deleted according to General Data Protection Regulation (GDPR)[1] of European Union. If medication is started, the participant will drop out from the study and the data collected until the decision to start medication will be collected.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria:	Exclusion criteria:
• 18 to 45 years • GDM diagnosis at GW 24-28	• type 1 or type 2 diabetes • use of medication that influences glucose metabolism (such as continuous therapy with oral corticosteroids or metformin) • multiple pregnancy • physical disability • current substance abuse • severe psychiatric disorder (that complicates participation to the study) • significant difficulty in cooperating (e.g., inadequate Finnish language skills).

Recruitment and consent

Participants are recruited from antenatal clinics from the Helsinki metropolitan area at GW 24-28. Local nurses at the municipal maternal clinics in Helsinki, Espoo and Vantaa inform about the possibility to participate in the eMOM GDM study in peer-support groups and share flyers in one-to-one meetings. We started the recruitment in 3/2021 and we plan to continue until 01/2023. Women who agree to participate sign two consent forms, one copy for themselves and one for the study nurse.

Blinding

For each block (see Section *Participants*), envelopes consisting of equal number of intervention and control cases were created for blinding. Based on the participant's status, a

[1] https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32016R0679&from=EN#d1e2001-1-1

study nurse opens a sealed envelope from the respective block. The content of the envelope determines whether the participant is assigned to the intervention or to the control group. This approach balances the allocation of subgroups of participants to intervention and control groups in a blinded manner.

Description of the eMOM GDM app and its wearable sensors

The eMOM GDM app and its integration to the medical personnel user interface (UI) was developed in 2020. The eMOM GDM app visualizes lifestyle data (physical activity, sleep, and nutrition) together with tissue glucose data in a single view (see figure 2A and figure 2B). For displaying the data, the eMOM GDM app has two views, a week view (see figure 2A) and a day view (see figure 2B). The information from the sensors and food tracker is updated each 10 min to the eMOM GDM app. We included an information section regarding pregnancy and GDM (see figure 2C). Based on recent studies [20,21] providing reliable information about how to manage GDM (particularly what to eat and how the fetus is developing) should be integrated in the GDM apps, so that no separate app for this is needed.

Medtronic Guardian Connect CGM with Enlite sensor (Medtronic, Dublin, Ireland; see figure 3) continuously measures tissue glucose. Flexible filament is inserted just under the skin to measure glucose levels in interstitial fluid approximately every 5 minutes. The eMOM GDM app shows these detailed glucose values when tapping the glucose curve on the screen (see figure 2D). Glucose values are sent to the mobile phone via Bluetooth. Medtronic requires calibration of the sensor by capillary blood glucose measurements 2 times a day.

Garmin Vivosmart 3 (Garmin International, KA, USA; see figure 3) is a wrist-worn optical heart rate and activity tracker which measures activity, sleep, and heart rate continuously based on its optical heart rate sensor, and 3D acceleration. Garmin Vivosmart 3 has been found to be feasible amongst pregnant women with good ratings on user experience [24] and

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measures steps well at slow walking speeds [25]. The tracked parameters include steps, estimated energy expenditure in calories (based on motion and heart rate), stairs, walking and running distance, all-day heart rate and stress. It connects automatically to a mobile app (Garmin Connect) and data is stored automatically to the cloud, where it can be accessed via application programming interfaces (APIs).

A dedicated food-tracker was developed by Helsinki University Hospital to make the food intake data collection easier for pregnant women. A user enters the time of each meal, food items consumed and portion sizes to the food-tracker. The food-tracker fetches the food items and their nutrient contents from Fineli food composition database[2], calculates nutrient intake and shows the amounts of the energy yielding nutrients and fiber to the user. This data is transferred to the eMOM GDM app where the energy intake from each energy yielding nutrient is visualized as stacked bars (see figure 2B). More detailed information (recorded food items, nutrient intake in grams) can be accessed (see figure 2E) by tapping the stacked bar (see figure 2B). In addition, participants were asked to add their weight to the eMOM GDM app once a week.

figure 2. Screenshots of main views in the eMOM GDM app. A) a week view for self-tracking data (Copyright: Fujitsu Finland), B) a day view for self-tracking data (Copyright: Fujitsu Finland), C) pregnancy and GDM related information (Copyright: Helsinki University Hospital), D) detailed glucose view (Copyright: Fujitsu Finland), and E) detailed nutrition view (Copyright: Fujitsu Finland).

[2] Finnish National Institute for Health and Welfare, http://www.fineli.fi

Standard care for both groups

All participants in the study receive standard care, in addition to the study protocol. The public health care system in Finland offers all pregnant women antenatal health care on a regular basis in municipal maternity clinics at primary health care centers. A doctor and a nurse are following the pregnancy in collaboration. Sessions are divided into periodic audits (basic visits) and discretionary additional visits. The periodic health check includes a minimum number (9-10) of visits with a nurse, and two doctor examinations designed for normal, low risk pregnancies. The first medical check-up is during GW 8-10. Maternity clinics and hospitals have provided detailed instructions on when the mother should be sent to the hospital for further examinations and follow-up [26].

A 2h-OGTT is performed normally at GW 24-28, but if the risk of the GDM is considered high (BMI >35kg/m^2, previous GDM, glycosuria in early pregnancy, incidence of type 2 diabetes in grandparents, parents or siblings, oral corticosteroid therapy, polycystic ovary syndrome), OGTT is performed already at GW 12-16. After a GDM diagnosis, the women receive guidance on diet, physical activity, and self-monitoring of blood glucose with electronic capillary glucose meters [23]. In case of repeated fasting capillary glucose of ≥5.5 mmol/l or a one-hour postprandial value of ≥7.8 mmol/l, the maternity clinic refer the woman to a maternity hospital for further assessment regarding need of medication [23].

Objectives and hypotheses

The principal aim of the study is to evaluate the effect of the eMOM GDM application on maternal glucose levels by comparing intervention and control groups. We also study the effects of the application on different other maternal and neonatal outcomes (please see the specific objectives below). The follow-up visit after the delivery and intervention takes place 3 months postpartum.

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The specific objectives of the intervention study are to compare between the intervention and the control groups:

1. Differences in maternal glucose levels during pregnancy,
2. differences in physical activity and stress levels during pregnancy,
3. differences in total diet during pregnancy,
4. difference in the need for medication due to GDM,
5. difference in gestational weight gain (GWG),
6. birthweight, incidence Large-for-Gestational-Age (LGA) and macrosomic (birthweight >4000g) newborns, and infant's body composition,
7. differences in motivation during the pregnancy, and
8. differences in physical activity, total diet, weight retention and glucose values 3 months postpartum.

Main hypothesis: Fasting plasma glucose, between baseline (BL) and GW 35-37, will decrease more in the intervention than in the control group.

Outcomes

Primary outcome is the change in fasting plasma (fP)-glucose from BL (GW 24-28) to GW 35-37. The main secondary outcomes are given in Table 2.

Table 2. The main secondary outcomes.

The main secondary outcomes
1. Difference in capillary fasting glucose and 1-h postprandial glucose values during pregnancy, 2. difference in capillary glucose area under the curve (AUC) during pregnancy, 3. change in Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) during pregnancy and 3 months postpartum, 4. difference in physical activity level during pregnancy and 3 months postpartum, 5. difference in total diet during pregnancy and 3 months postpartum, 6. difference in medication use due to GDM (insulin, metformin), 7. difference in GWG and postpartum weight retention, 8. difference in birthweight (SD) of child, 9. difference in LGA of child and macrosomia,

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10. difference in infant's body composition,
11. difference in neonatal hypoglycemia (<2.6 mmol/l) incidence within a week from birth,
12. difference in motivation to manage GDM during pregnancy, and
13. difference in fP-glucose and 2-hour blood glucose levels measured with OGTT (75g) at 3 months postpartum.

Measurements

We take measurements with multiple techniques and sensors. All the measurements, except measurements specific to the eMOM GDM app intervention are taken from both groups (see a summary in Table 3).

Table 3. Measurements for intervention and control groups:

Measurements for intervention and control groups:	**Baseline GW 24-28**	**III trim GW 35-37**	**Birth**	**Postpartum (3 months)**
○ Background questionnaire	•			
○ OGTT	•			•
○ Capillary glucose measurements	•	•		
○ Laboratory blood samples	•	•		•
○ Questionnaires*	•	•		•
○ Physical activity (UKK RM42 - accelerometer)	•	•		•
○ Heart rate variability (Firstbeat Bodyguard 2) (analyses shown to participants only after postpartum visit)	•	•		•
○ Cord blood			•	
○ Placental weight			•	
○ Infant's anthropometry (Pea Pod)			•	
Measurements only for intervention group:				
○ Data from sensors and apps: the eMOM GDM app, Garmin Vivosmart, Medtronic CGM, food tracker ○ Technology acceptance questionnaire (UTAUT-technology)	1 app week + 3 normal care weeks repeatedly until delivery			
○ Usability questionnaire	•			
○ Semi-structured interview**		•		

* *Questionnaires*= Food frequency questionnaire (FFQ), depression, motivation, and quality of life. At the postpartum study visit (3 months) FFQ and depression questionnaire.

** 20 participants will conduct the semi-structured interview about the user experience with the eMOM GDM app

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Background information

Age, BMI, parity and previous GDM status are collected from hospital registries, and socioeconomic status (e.g., education, occupation), alcohol use, possible special diet, and experience with self-tracking from a background questionnaire.

Maternal glucose levels

Maternal glucose levels are collected in the intervention and the control groups with three measurement types; (1) 2h- OGTT at GW 12-16 (early) or GW 24-28 (late) as well as 3 months postpartum, (2) capillary glucose measures (e.g. fasting glucose, postprandial glucose, AUC) (Contour Next One, Ascensia Diabetes Care, Basel, Switzerland) from BL until delivery, and (3) laboratory fP-glucose, HbA1c, fP-insulin at study visits at BL, GW 35-37, and 3 months postpartum Additionally in the intervention group, glucose levels are collected with a CGM (Medtronic Guardian Connect) 1 week/month from BL to delivery.

Maternal physical activity

Maternal physical activity is extracted from both groups at BL, GW 35-37, and 3 months postpartum with two "blind" sensors: UKK RM 42 and Firstbeat Bodyguard 2 (see figure 2). Movement is measured with UKK RM42 (UKK Institute, Tampere, Finland). It is a triaxial accelerometer that measures the device movement located either at the hip during waking hours and at the wrist during the time in bed for sleeping (see Sensor 4 in figure 3). The data analysis is based on validated MAD-APE algorithms [27,28]. The amount of daily physical activity is described in durations and intensity in METs, the amount of sedentary behavior (lying, sitting, and standing) in durations, and sleep as movement categories. These analyses have been employed in population-based studies of Finnish adults [29,30].

Heart rate variability (HRV) is measured with Firstbeat Bodyguard 2 sensor (Firstbeat Technologies, Jyväskylä, Finland) which is a chest worn wearable device which measures beat-to-beat heart rate variability and activity (3D acceleration) continuously for three days.

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The device is attached to the chest with two disposable clinical grade ECG electrodes (see Sensor 1 in figure 3). The device is able to continuously measure beat-to-beat heart rate variability with <3ms error and >99.9% detection rate as compared to clinical grade ECG [31]. Proprietary analytics software (Firstbeat Lifestyle Assessment, Firstbeat Technologies, Jyväskylä, Finland) is used to transform the recorded beat-to-beat and motion data into continuous assessment of energy expenditure, VO_2, physical activity, stress, and recovery. The methods has been validated widely in several studies including [32,33].

Physical activity measures are also collected in the intervention group with activity bracelet Garmin Vivosmart 3 one week/month from BL until delivery (see Sensor 3 in figure 3 and Section *Description of the eMOM GDM app and its wearable sensors*).

figure 3. The sensors used in the study. The sensors on the left (1. HRV sensor and 4. Movement sensor) are worn by both control and intervention group. The Movement sensor is a small box, which is attached either to a belt or to a bracelet. Sensors on the right (2. CGM and 3. Activity bracelet) are part of the intervention.

Maternal nutrition

We measure maternal total diet including food consumption and nutrient intake among intervention and control women during the preceding month with a digital semiquantitative 142-item food-frequency-questionnaire (FFQ) (updated from [34]) at BL, GW 35-37, and 3 months postpartum. FFQ is used for intervention effect estimation. Nutritional outcomes include e.g., intake of fruits and vegetables, wholegrain cereals, sugar, protein, carbohydrates, fiber, unsaturated and saturated fat, vitamins, and minerals. Additionally, participants in the intervention group are instructed to keep an electronic food diary for 3 days/month while they are wearing the CGM.

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Maternal gestational weight gain and weight retention 3 months postpartum

Weights (in kg) are extracted from the maternity card and at study visits at BL and GW 35-37, within 2 days after birth, and 3 months postpartum.

Neonatal outcomes

Neonatal anthropometric measures at birth are extracted from hospital registry; birthweight (SD), birth length, incidence of LGA/macrosomic newborn (>+2SD / >4000g), and newborn body composition (body fat%, lean body mass%) by Pea Pod (COSMED, Italy, Rome) air-displacement plethysmography [35–37] within 2 days after birth. Also, Apgar scores, neonatal hypoglycemia (<2.6 mmol/l), transfer to intensive care and intravenous glucose infusion of newborn are collected.

Psychological factors, motivation, and health-related quality of life

Maternal depression and health-related quality of life are collected with the digital questionnaires at BL, GW 35-37, and 3 months postpartum. Motivation is collected with the digital questionnaires at BL and GW 35-37. Depression is measured with Edinburgh depression postnatal depression scale (EPDS) [38], which is also used during pregnancy (e.g., [39]), health-related quality of life with 15D questionnaire [40], and motivation with Treatment Self-Regulation Questionnaire (TSRQ) [41] and Perceived Competence for Diabetes Scale (PCDS) [41]. The digital questionnaire data is collected through Qualtrics[3] (Qualtrics International Inc., Seattle, United States).

Measures about the intervention

We measure the app usage by logging the time and type of every interaction with the eMOM GDM app. Human factors relating to app use are measured with Unified Theory of Acceptance and Use of Technology (UTAUT) questionnaire [42], Software Usability

[3] www.qualtrics.com

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Measurement Inventory (SUMI) [43], and with a semi-structured interview on user experience with the eMOM GDM app with randomly selected twenty participants.

Data analysis

We will analyze the data using RStudio (Version 1.1.456, RStudio, Boston, USA) and perform the analyses according to intention-to-treat principle. Missing data will not be replaced. For comparing maternal outcomes and neonatal outcomes between intervention and control group we will use classical statistical tests (such as t-test, χ^2-test, and ANCOVA) depending on type of the variable and its distribution (i.e., normality and homogeneity). The comparisons of changes between the control and the intervention group will be performed using either ANOVA of change from baseline or ANCOVA, having the BL measurements as covariate [44]. The selection depends on the possible differences at baseline [44]. Other maternal covariates will be maternal socioeconomic situation (education, occupation), age at childbirth, BMI, parity, and smoking during pregnancy. The birthweights will be adjusted according to Sankilampi et al. [45]. Regarding the eMOM GDM app use, we will investigate correlations between usage patterns of the eMOM GDM app and outcomes (maternal and neonatal). We will conduct a cluster analysis for the usage patterns to identify effective usage strategies of the eMOM GDM app similar to apps designed for type 2 diabetes management [46].

For the CGM data, we will conduct time series analysis using standard techniques [47], such as AUC and incremental AUC [48,49] and *mean amplitude of glycemic excursions* [50]. Interim data analysis will be performed by data analysis team (MK, LM, and PM) when the research data from a half of the participants (N=100) is being collected. Study nurses will remain blinded to the interim results, and we will blind the statistical analyses by asking an external person to recode the participants before conducting final analyses. The final dataset

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is accessed by data analysis team (MK, LM, and PM). The final decision to terminate the trial will be made by the principal investigator (SK).

Sample size

To detect at least a 0.32 mmol/l between-group mean difference in the fP-glucose (primary outcome) response to the intervention ($\alpha<0.05$, power=95%, an assumed dropout rate of 40%), a sample of 200 women (100 in each intervention arm) is needed for the intervention study. This anticipated difference of 0.32 mmol/l between the intervention group and control group corresponds to 0.7 SD of variation in fP-glucose change observed previously in similar women and stage of pregnancy (SD needed for power calculation has been calculated from the Finnish Gestational Diabetes Prevention Study -population; SD for change in fP-glucose value between II and III trimesters in women who got GDM diagnoses at II trimester) [51].

eMOM GDM system implementation and data maintenance

The system implementation was designed to support wider employment of eMOM GDM service concept as a part of future digital health care path for women with GDM in Helsinki metropolitan area. Technical implementation of the eMOM GDM app as well as browser-based UI for health care professionals were conducted by Fujitsu Finland Oy. The data transfer to the eMOM GDM app and professional UI is implemented in the cloud so that eMOM app's back-end server fetches data from a data integration server. Data integration server (implemented by Elisa Corp.) gathers data from sensors' and food tracker's cloud services. The data from eMOM GDM service's back-end server is further transferred to secure HUS Data Lake environment (Microsoft HDInsight Hadoop cluster).

Feasibility study

Before this RCT trial, we conducted feasibility studies of the eMOM GDM app, wearable sensors and food-tracker involving women with GDM (data not published yet). The digital

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food-tracker used in this study was originally speech-enabled, but in the feasibility study we noticed that a large majority of participants preferred typing over speech. Thus, we discontinued the support for speech recognition.

Ethics and dissemination

The eMOM GDM study is in accordance with the Declaration of Helsinki[4]. All the participants sign informed consent forms, and they are instructed that they can withdraw at any point during the study. Data during any processes or analyses is pseudonymized, and it does not contain personal information that could be directly linked to any individual. For example, a participant of the intervention group gets a pseudonym (ID based) email address, which the participant uses when she logs in to the eMOM GDM app and the sensor-associated apps. We have ethical approval from ethical committee of HUS, and study permissions from three cities (Helsinki, Espoo, and Vantaa) in the Helsinki Metropolitan area to recruit participants.

As a part of quality assurance, the study is being monitored by an external institution, Helsinki University Central Hospital's Study Monitor of Clinical Research Institute[5], according to legislation, official guidance, and good clinical practice (GCP)[6]. The auditing visits are conducted every 6 months during the trial, and the auditing process is independent from investigators and the sponsor.

Important protocol modifications will be communicated with research group, Ethical committee of Helsinki University Hospital, and ClinicalTrials.gov.

Sponsor provides facilities for the trial and funder partly funds the trial, but they do not have role in study design. There are monthly technical steering group meetings by project partners,

[4] www.wma.net
[5] https://hyksinstituutti.fi/clinical-research-institute-huch/?lang=en
[6] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice

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in which the progress of the trial is followed. However, the ultimate authority to make decisions regarding the clinical trial is principal investigator (SK).

The results of the eMOM GDM study will be published in peer-reviewed journals and at national and international scientific conferences. We promote open science by blogs and interact actively with the media, including social media (e.g., Twitter and LinkedIn), to gain visibility to our findings among journalists and among non-research community as well.

Patient and Public Involvement Statement

Both women with GDM and registered nurses from the Helsinki Metropolitan Area were involved in the design process of the eMOM GDM service concept. Based on the feedback from the use of the first version of the eMOM GDM app, it was modified into version which is used in the eMOM GDM clinical trial. The user-centered design process involved women with GDM (N=21) who did not participate in the clinical trial and the results will be published in a separate article. The local nurses gave insights into the design of the professional UI.

Adverse events

All participants will be under standard care, and thus will be in close medical observation. In the case of adverse or harmful events, study nurses will report to principal investigator (SK) and the appropriate response to these will be discussed within the research group. All participants are insured with the patient injury insurance by Helsinki University Hospital.

DISCUSSION

Our approach differentiates from existing GDM app interventions in three main aspects. First, we have wearable sensors integrated with the eMOM GDM app. This enables viewing self-tracking data in one place. Objectively and automatically measured, and constantly available

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data through wearable sensors data can be expected to support learning. However, learning through self-tracking requires active agency from women with GDM, as associations between lifestyle and nutrition are complex and difficult to identify, especially within first weeks after the GDM diagnosis [52]. Thus, it remains to be seen if this type of feedback, being quite different from what women with GDM receive in standard care, is effective enough for improving maternal glycemic levels and neonatal outcomes. Secondly, our intervention differentiates from other app-based interventions in timewise. Our intervention has clearly defined instructions when participants should use the app (one week per month) and keep food diary (3 days per month). These time periods were chosen based on the validity (3-day food diary have shown to provide equally valid results with 9-day food diary [53]), decrease of engagement with mHealth over time [54], practicality (battery of CGM lasts approx. a week), and costs (the price of the sensors; we were able to rotate them amongst participants). The effects of this type of periodical intervention remain unclear, and we will collect experiences on this with interviews with the participants. Thirdly, the system does not consist of an app only, as there is UI for professionals to view the data from the CGM, activity bracelet and food diary from each participant in the intervention group. In this study, the professional UI is used only for remote monitoring of the technical data flow from the participants in a real-time. In the future, the professional UI is planned to be used as a resource for monitoring and giving guidance for women with GDM. Together with the eMOM GDM app, the professional UI forms a novel service concept, which can be employed as future digital health care path for women with GDM.

The comprehensive self-tracking approach also poses challenges. As we are utilizing multiple sensors and they have their own apps, it is difficult to identify how much the eMOM GDM app and other apps (CGM's app and activity bracelet's app) influence the learning. Especially, the CGM solely has been identified to facilitate self-discovery, i.e., finding

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associations between lifestyle (e.g., nutrition) and glucose levels [55,56]. In order to evaluate the eMOM GDM app's role, we will log the interactions with the app, and we will interview a subgroup of participants about the user experience with the app. By doing so, we are able to evaluate the compliance and engagement with the app, which has been identified as a shortcoming in studies evaluating the effectiveness of GDM apps [19]. The other challenges emerge from technical implementation and maintenance. The sensors' apps need to be installed in compatible mobile phones and the data is fetched to the eMOM GDM app through APIs in the cloud services. This requires active monitoring for the updates regarding compatibility issues between phones and sensors and their APIs.

Contributors

SK, SH, MK, PM, GJ planned the design of the study. MK, LM, PM, and SK planned the analysis of the data and performed the power calculation. SN, SMV, TEK were responsible of methods of dietary data collection and calculations. HS, HV-Y, and IK designed the collection of physical activity data. MK and SK wrote the draft and all authors MK, SK, LM, PM, GJ, SN, SMV, HS, HV-Y, IK, TEK, SH have reviewed and approved the final manuscript.

Conflicts of interests

IK is a shareholder of Firstbeat Technologies and products of Firstbeat Technologies are used in the present study. These are sold on commercial basis to researchers. Firstbeat does not fund or supervise the study as an organization

Funding

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Data sharing statement

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All data will be collected in Helsinki University Hospital Datalake from where pseudo-anonymised data can be requested until 2032 via a data sharing contract. Proposals should be directed to tietopalvelu(a)hus.fi.

Ethics Approval

The Ethics Committee of the Helsinki and Uusimaa Hospital District has accepted the study protocol (HUS-2165-2018-3).

Acknowledgments

We gratefully acknowledge the contribution of Fujitsu Finland Oy for the technical implementation of eMOM app and Elisa for sensor integration. We wish to thank all the women with GDM in Finland taking part in the research so far, and the study nurses Jaana Palukka, Sanna Lampi and Milla Tuhkanen.

Provenance and peer review

Not commissioned; externally peer reviewed.

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Protocol date

May 27, 2022

Sponsor

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Helsinki University Hospital

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figure 1. Design of the randomized controlled trial.

figure 2. Screenshots of main views in eMOM app. A) a week view for self-tracking data (Copyright: Fujitsu Finland), B) a day view for self-tracking data (Copyright: Fujitsu Finland), C) pregnancy and GDM related information (Copyright: Helsinki University Hospital), D) detailed glucose view (Copyright: Fujitsu Finland), and E) detailed nutrition view (Copyright: Fujitsu Finland).

figure 3. The sensors used in the study. The sensors on the left (1. HRV sensor and 4. Movement sensor) are worn by both control and intervention group. The Movement sensor is a small box, which is attached either to a belt or to a bracelet. Sensors on the right (2. CGM and 3. Activity bracelet) are part of the intervention.

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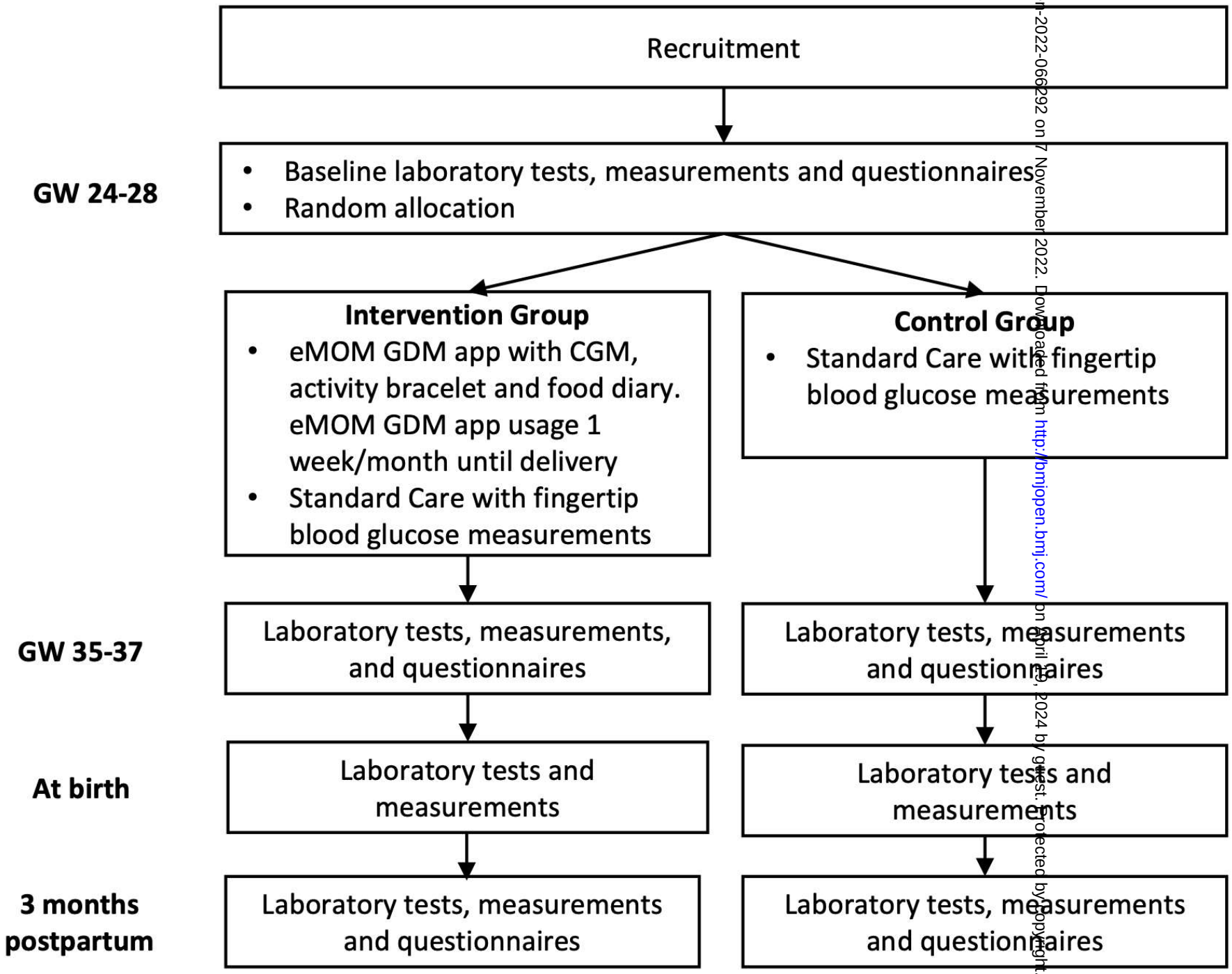

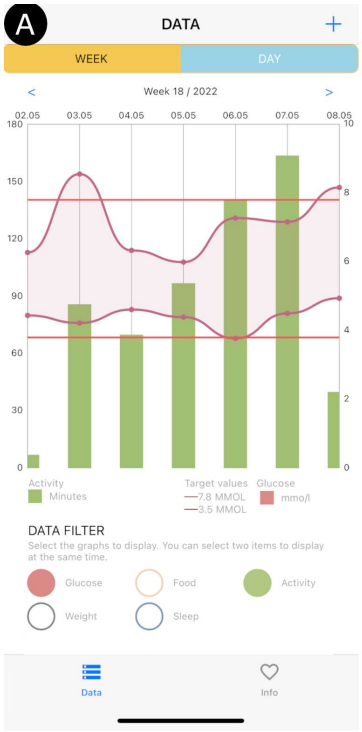

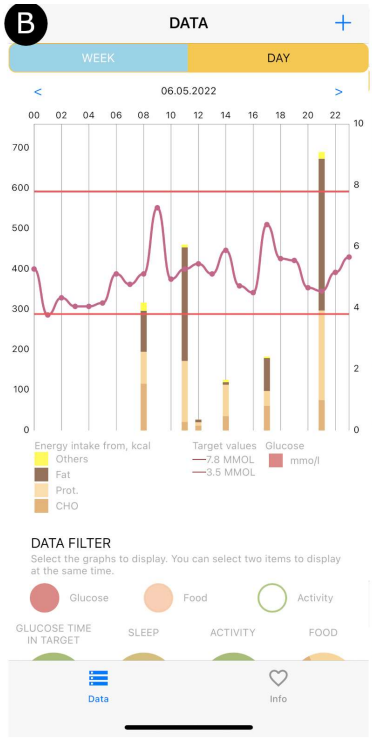

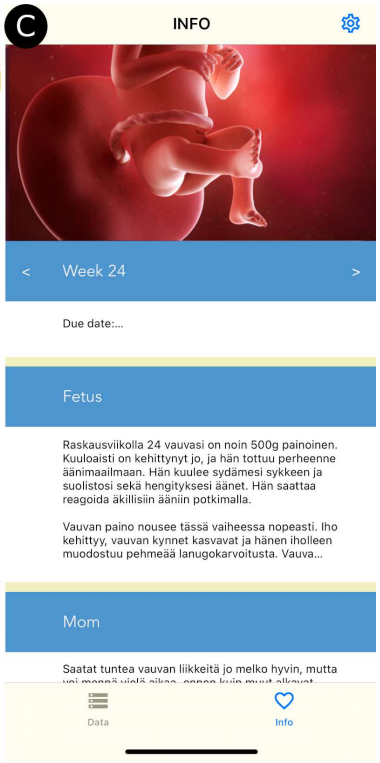

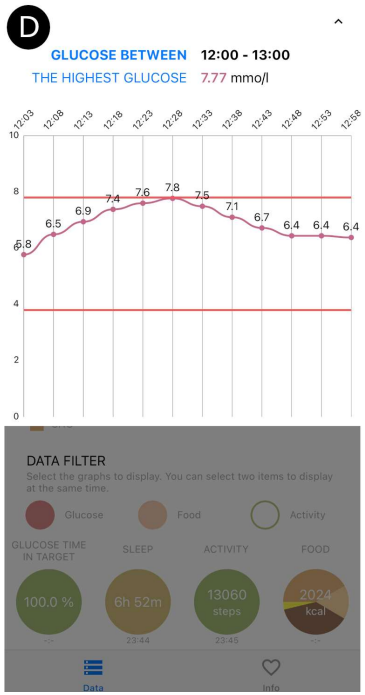

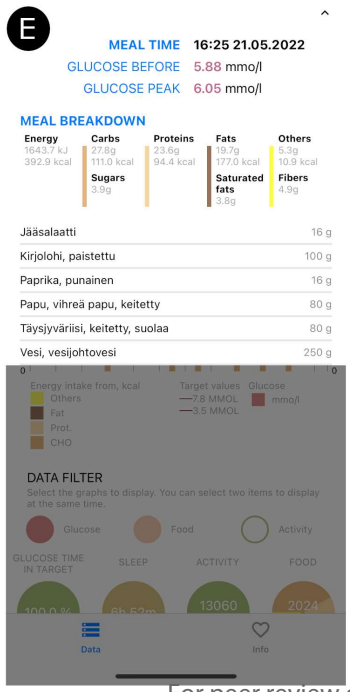

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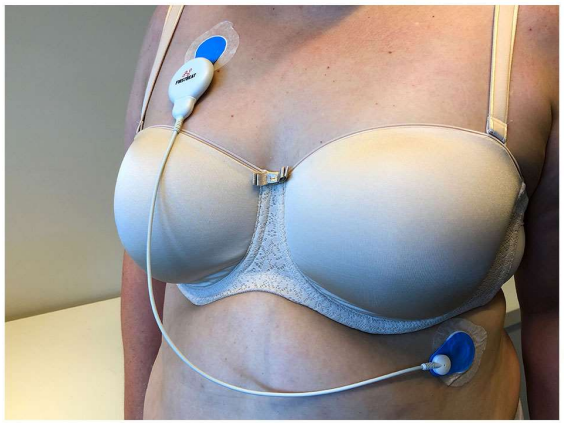

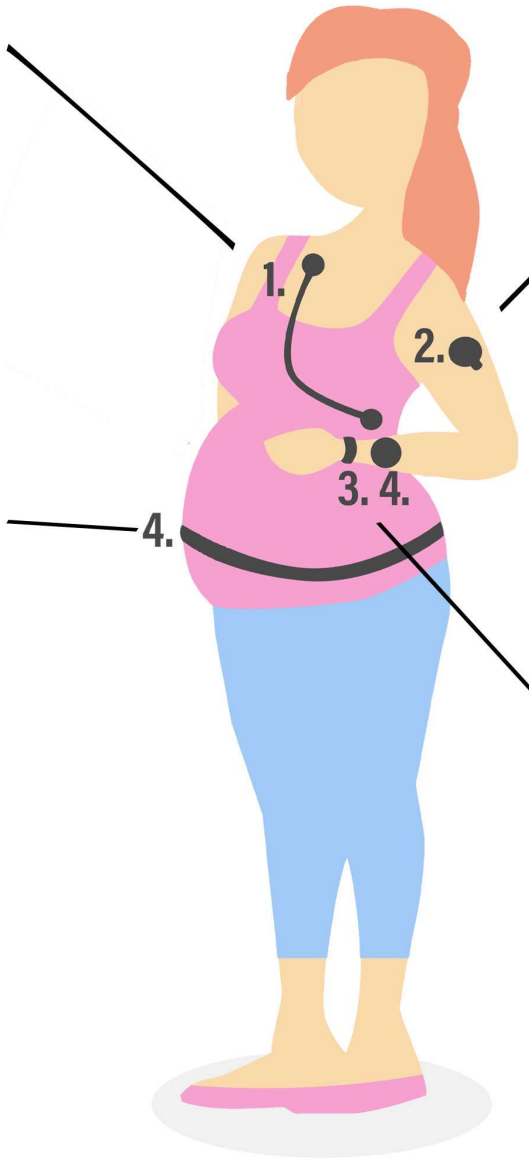

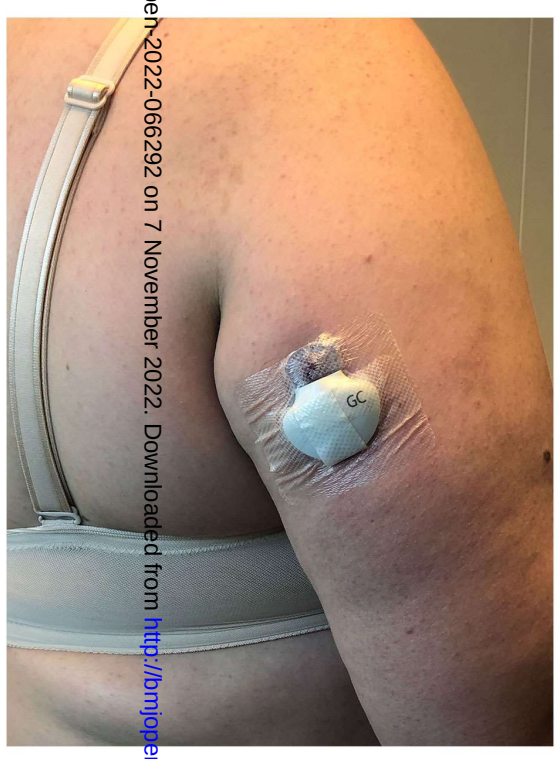

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Reporting checklist for protocol of a clinical trial.

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		Reporting Item	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	3

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		registered, name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	20
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,19
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	20
Roles and responsibilities: sponsor and funder	#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	16
Roles and responsibilities: committees	#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,	16

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		if applicable (see Item 21a for data monitoring committee)	
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	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	8-9
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, non-inferiority, exploratory)	4
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

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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: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
Interventions: modifications	#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)	5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
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	9

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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)	see figure 1
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	14
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	#16b	Mechanism of implementing the allocation	6

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concealment mechanism		sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A, Data will be blinded to data analysts and there is no need to reveal the allocation for the analysis.
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related	9-13

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		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	
Data collection plan: retention	#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	5
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	14-15
Statistics: outcomes	#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	13-14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis	#20c	Definition of analysis population relating to protocol	13

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population and missing data		non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring: formal committee	#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	15-16
Data monitoring: interim analysis	#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	14
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	17
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16-17
Ethics and dissemination			

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Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	3
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)	16
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A, not applicable.
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14-15
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14

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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	17
Dissemination policy: trial results	#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	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A, we have no authorship eligibility guidelines and we don't intend to use professional writers.
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Added as supplemental material.

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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	N/A, we have no such intentions.

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