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Maternity Log study: a longitudinal lifelog monitoring and multiomics analysis for the early prediction of complicated pregnancy

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ABSTRACT

Purpose A prospective cohort study for pregnant women, the Maternity Log study, was designed to construct a time-course high-resolution reference catalogue of bioinformatic data in pregnancy and explore the associations between genomic and environmental factors and the onset of pregnancy complications, such as hypertensive disorders of pregnancy, gestational diabetes mellitus and preterm labour, using continuous lifestyle monitoring combined with multiomics data on the genome, transcriptome, proteome, metabolome and microbiome.

Participants Pregnant women were recruited at the timing of first routine antenatal visits at Tohoku University Hospital, Sendai, Japan, between September 2015 and November 2016. Of the eligible women who were invited, 65.4% agreed to participate, and a total of 302 women were enrolled. The inclusion criteria were age ≥20 years and the ability to access the internet using a smartphone in the Japanese language.

Findings to date Study participants uploaded daily general health information including quality of sleep, condition of bowel movements and the presence of nausea, pain and uterine contractions. Participants also collected physiological data, such as body weight, blood pressure, heart rate and body temperature, using multiple home healthcare devices. The mean upload rate for each lifelog item was ranging from 67.4% (fetal movement) to 85.3% (physical activity), and the total number of data points was over 6 million. Biospecimens, including maternal plasma, serum, urine, saliva, dental plaque and cord blood, were collected for multiomics analysis.

Future plans Lifelog and multiomics data will be used to construct a time-course high-resolution reference catalogue of pregnancy. The reference catalogue will allow us to discover relationships among multidimensional phenotypes and novel risk markers in pregnancy for the future personalised early prediction of pregnancy complications.

INTRODUCTION

The incidence of pregnancy-related disorders, including hypertensive disorders of pregnancy (HDP), gestational diabetes mellitus (GDM) and preterm delivery has been increasing worldwide.1–4 These multifactorial conditions are caused by an interaction of genetic factors and environmental factors.5 6 Recent reports suggest that continuous lifestyle monitoring using wearable biosensors provides important information on latent physiological changes that are exhibited prior to the onset of disease.7 Using these monitors, environmental factors may be estimated more accurately than by using conventional questionnaires.
For these reasons, we have designed a prospective cohort study for pregnant women, the Maternity Log study (MLOG). In this study, pregnant women upload daily information and physiological data using multiple home healthcare devices. In addition, a variety of biospecimens are collected for multiomics analysis.

To the best of our knowledge, this study will be the first to integrate multiomics analyses and objective data on environmental factors, including daily lifelog data, in pregnant women. This study may demonstrate correlations between specific lifelog patterns and pregnancy-related physiological changes, such as blood pressure, gestational weight gain and onset of obstetric diseases. Furthermore, studies on associations among lifelog patterns, plasma and urine metabolomes, transcriptomes and genomic variations may reveal relationships among multidimensional phenotypes and lead to identification of novel risk markers in pregnancy for the future personalised early prediction of pregnancy complications, for example, HDP, gestational diabetes and preterm labour.

### COHORT DESCRIPTION

#### Study setting

The aim of the MLOG study is to construct a time-course high-resolution reference catalogue of bioinformatic data in pregnancy and thereby develop methods for early prediction of obstetric complications, through integrated analysis of daily lifelogs and multiomics data, that is, maternal genomes, transcriptomes, metabolomes and oral microbiomes. The MLOG study is a prospective, add-on cohort study, built on a birth-generation and three-generation cohort study established by the Tohoku Medical Megabank Organization (ToMMo) (TMM BirThree Cohort Study) in order to elucidate the mechanisms of complicated multifactorial diseases in mothers and children in the wake of the Great East Japan Earthquake in 2011. Epidemiological data from extensive questionnaire surveys and accurate clinical records, including birth outcomes, can be abstracted from the integrated biobank of the ToMMo.

TMM BirThree Cohort Study was started in July 2013 in one obstetric clinic and expanded throughout Miyagi Prefecture, and approximately 50 obstetric clinics and hospitals (including Tohoku University Hospital) participated in the recruiting process. We planned to recruit 20000 pregnant women as probands, and her family members from three generations, which is a total of over 70000 participants. Written informed consent was obtained from all participants by the genome medical research coordinators (GMRCs).

#### Patient and public involvement

Patients or the public were not directly involved in the development of the research question or the design of the study. The main results will be made available in the public domain.

### Participants

Participants were recruited at a first routine antenatal visit at Tohoku University Hospital, Sendai, Japan, between September 2015 and November 2016. A flow chart of the recruitment process is shown in figure 1. GMRCs at Tohoku University Hospital approached eligible pregnant women for TMM BirThree Cohort Study (n=631), and patients who already agreed to participate in TMM BirThree Cohort Study (n=513) were assessed for eligibility for the MLOG study. Finally, 462 pregnant women were asked to provide informed consent for the MLOG study. A total of 302 women were enrolled. The inclusion criteria were the age ≥20 years and the ability to access the internet using a smartphone in the Japanese language. Participants were excluded after enrolment if termination of pregnancy, abortion or transfer to another institution for emergency care occurred before delivery, or if they withdrew consent for any reason.

#### Outline of study protocol

The study protocol consisted of blood and urine sampling, saliva and dental plaque sampling, self-administered daily lifelog data collection and data upload from multiple healthcare devices through a smartphone. An overview of the protocol is provided in figure 2. In Japan, routine antenatal visits, including ultrasounds, are scheduled every 4 weeks from early pregnancy (<12 weeks) to 23 weeks of gestation, every 2 weeks from 24 weeks to 35 weeks and every week from 36 weeks to delivery. Lifelog data collection was continued throughout pregnancy and until 1 month after delivery. Optional data collection could be continued up to 180 days after delivery.

#### Blood and urine sampling

Blood samples were collected three times from each participant; the first sample was collected between 12 weeks and 24 weeks of gestation, the second between 24 weeks and 36 weeks, and the third at 1 month after delivery. A maximum of 15mL of blood was collected each time, from which serum and plasma were separated to be stored at −80°C until the time of analysis. An aliquot of blood (2.5mL) was stored in a PAXgene tube (Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA) at −80°C until the time of RNA extraction for transcriptome analysis. Genomic DNA was extracted from mononuclear cells using an AutoPure extractor (Qiagen, Venlo, The Netherlands). Approximately 10mL of cord blood was collected from the umbilical vein in a PAXgene tube for storage at −80°C and in an EDTA 2K tube (Becton, Dickinson and Company) for separation of plasma to be stored at −80°C. Urine samples (10mL) were collected at each antenatal visit; when participants were admitted to the hospital ward, urine was collected once weekly. Urine samples were immediately transferred and stored at −80°C until the time of analysis.
Saliva and dental plaque sampling
Samples of saliva and dental plaque were collected three times from each participant, at the same time points as blood collection. Approximately 3mL of saliva was collected using a 50mL conical centrifuge tube (Corning, Inc, Corning, New York, USA) and stored at −80°C until analysis. Dental plaque was sampled by brushing, suspended in 0.5mL of Tris-EDTA (10mM Tris, 1mM EDTA; pH, 8.0) and immediately stored at −80°C until the time of sample processing.

Lifelog data collection
Based on previous publications on the utility for risk assessment of pregnancy-related diseases, we selected several lifelog parameters to employ in this study, that is, body temperature,10 home blood pressure,11 body weight12 and physical activity (calorie expenditure),13 as well as self-administered information such as sleep quality,14 condition of stool using the Bristol Scale21–23; severity of nausea using the Pregnancy-Unique Quantification of Emesis and nausea (PUQE) score24 25; headache, toothache, lumbago and upper and lower abdominal pain using a numerical rating scale (NRS) score; the number of perceived uterine contractions; palpitations; and fetal movement using a modified count-to-10 fetal movement chart.26 27

Sleep quality was evaluated by the wakeup time, bedtime, sleep satisfaction (ranked from satisfied to poor using a numeric scale of 0–4) and the number of nocturnal awakenings (0–6).

The Bristol stool form scale was originally developed to assess constipation and diarrhoea,21 22 and its use has been spread widely to evaluate functional bowel disorders.22 Using the Bristol scale, stool is classified into seven types according to cohesion and surface cracking.21 22
The PUQE score\textsuperscript{24,25} was developed to estimate the severity of nausea and vomiting in pregnancy and quantifies the number of daily vomiting and retching episodes and the length of nausea in hours (over the preceding 12 hours). The total score ranges from 3 (no symptoms) to 15, and higher scores are correlated with increasing severity of nausea and vomiting\textsuperscript{24,25}.

In the NRS score for headache, toothache, lumbago and upper and lower abdominal pain, the total score ranges from 0 (no pain) to 10 (maximum ever experienced).

Uterine contractions and palpitations were evaluated using definitions determined for the current study. Uterine contractions were assessed using the number of perceived contractions per day, ranging from 0 to more than 5. The count-to-10 method was originally developed to assess fetal well-being by recording the time, in minutes, required to count 10 fetal movements.\textsuperscript{26} More recently, a modified count-to-10 method has been proposed: pregnant women are advised to start counting when they feel the first movement, then record the time required to perceive an additional nine movements.\textsuperscript{27} Pregnant women are encouraged to select a 2-hour period when they feel active fetal movements and are instructed to count kicking and rolling movements in a favourable maternal position after 24 weeks of gestation.

The applications also collected dietary logs and the medications taken on the day before and the day of the antenatal visit on which blood or urine samples were collected.

Daily home blood pressure, body weight, body temperature and physical activity were measured as described below with home healthcare devices and uploaded through wireless communications using mobile applications on a smartphone. Daily home blood pressure was measured twice daily using an HEM-7510 monitor (OMRON Healthcare, Kyoto, Japan): within 1 hour of
awakening in the morning and just before going to bed at night. Body weight was measured using an HBF-254C metre (OMRON Healthcare) once daily within 1 hour of awakening in the morning. Daily body temperature was evaluated using an MC-652LC digital thermometer (MC-652LC; OMRON Healthcare) just after awakening. Physical activity was assessed using an HJA-403C pedometer (HJA-403C; OMRON Healthcare) to count steps and calculate calorie expenditure.

Clinical and epidemiological information
Baseline clinical information and maternal and neonatal outcomes (eg, maternal age, clinical data and findings from each antenatal visit, gestational age at delivery, type of delivery, birth weight and maternal and fetal complications) were obtained from the medical records of Tohoku University Hospital. Epidemiological data, including extensive questionnaire surveys by TMM BirThree Cohort Study, can be obtained from the ToMMo integrated biobank.33

Database
A customised laboratory information management system (LIMS) was established to track all biospecimens. All data were transferred to the TMM integrated database after two-step anonymisation in a linkable fashion. Data handling was strictly regulated under Health Insurance Portability and Accountability Act of 1996 US Security and Privacy Rules28 29 and the Act on the Protection of Personal Information.30 Security control at our facility has been described previously.31

Omics analysis
Whole-genome sequencing
To minimise amplification bias, we adopted a PCR-free library preparation method. After preparing library quality control (QC) using the quantitative MiSeq method,32 libraries were sequenced on HiSeq 2500 Sequencing System (Illumina, San Diego, California, USA) to generate 259 bp, paired-end reads. We generated the sequencing data at over 12.5x coverage on average, and we identified variants using the alignment tool BWA-MEM (V.0.7.5a-r405) with the default option. Single nucleotide variants (SNVs) and indels were jointly called across all samples using Genome Analysis Tool Kit’s HaplotypeCaller (V.8). Default filters were applied to SNV and indel calls using the GATK’s Variant Quality Score Recalibration approach. The human reference genome was GRCh37/hg19 with the decoy sequence (hs37d5) and NC_007605 (Human Gamma Herpesvirus 4). The complete fasta file named hg19_tommo_v2.fa is available from iJGVD website (http://ijgvd.megabank.tohoku.ac.jp).33 For the quality assurance, we have checked the ratio of the bases with the phred quality score over 30, the total variant numbers in each chromosome and the ratio of transitions to transversions for a pair of sequences.

Transcriptome
Whole blood was collected using the PAXgene RNA tube, which is widely used for transcriptome analysis. After storage at −80°C, total RNA was purified with PAXgene Blood RNA Kit (Qiagen) using QiaSymphony (Qiagen). Total RNA was reverse-transcribed using an oligo-dT primer. We used TruSeq DNA PCR-Free Library Preparation Kit (Illumina) for library preparation for sequencing with HiSeq 2500 Sequencing System. For the quality assurance, we randomly selected 11 samples in one batch (usually 48 samples) and checked an RNA integrity number (RIN) (or an RIN equivalent) using BioAnalyzer or Tape Station (both from Agilent Technologies, Santa Clara, California, USA). The batch with RIN (or an RIN equivalent) higher than 7.0 for all tested samples was used for the downstream analysis. The minimum threshold for the total sequence reads for each sample was set to 30 million. For computing a series of QC metrics for RNA-seq data, RNA-SeQC was used to check the quality of sequence reads.34

Plasma and urine metabolome
Nuclear magnetic resonance (NMR) spectroscopy
All NMR measurements for metabolome analysis were conducted at 298 K on a Bruker Avance 600 MHz spectrometer equipped with a SampleJet sample changer (Bruker, Billerica, Massachusetts, USA).36 Standard 1-dimensional nuclear Overhauser enhancement spectroscopy and Carr-Purcell-Meiboom-Gill spectra were obtained for each plasma or urine sample. All spectra for plasma or urine samples were acquired using 16 scans and 32k of complex data points. All data were analysed using the TopSpin 3.5 (Bruker) and Chenomx NMR Suite 8.2 (Chenomx, Edmonton, Alberta, Canada) programmes. All spectra were referenced to an internal standard (DSS-d6). As necessary, those spectra were aligned using hierarchical cluster-based peak alignment method, which is implemented as an R package called ‘speaq’.36

Gas chromatography-tandem mass spectrometry (GC-MS/MS)
Sample preparation for plasma and urine (50 µL each) was performed using a Microlab STARlet robot system (Hamilton, Reno, Nevada, USA) followed by the methods previously reported by Nishiumi et al.37 38 The resulting deproteinised and derivatised supernatant (1 µL) was subjected to GC-MS/MS, performed on a GC-MSTQ-8040 system (Shimadzu, Kyoto, Japan). The compound separation was performed using a fused silica capillary column (BPX-5; 30 m×0.25 mm inner diameter; film thickness: 0.25 µm; Shimadzu). Metabolite detection was performed using Smart Metabolites Database (Shimadzu) that contained the relevant multiple reaction monitoring (MRM) method file and data regarding the GC analytical conditions, MRM parameters and retention index employed for the metabolite measurement. The database used in this study included data on 475 peaks from 334 metabolites. All peaks of metabolites detected from each sample was annotated and analysed using Traverse
MS (Reifycs, Tokyo, Japan). Then, two types of normalisation were performed to these annotated metabolites. The first normalisation was performed using the peak of 2-isopropylmalic acid as an internal standard, which was added to each sample before analysis with GC-MS/MS. Then the second normalisation was performed using QC samples, which were injected after every 12 study samples according to the reference quality control (RQC) normalisation methods. Normalised values of each metabolite in the QC samples were assessed by calculating coefficients of variation (CVs), and metabolites with CVs over 20% were eliminated.

**Oral microbiome**

Analysis of oral microbiome was conducted by previously reported protocols. In brief, saliva was collected in a 50mL tube. Dental plaque was sampled by participants by brushing teeth with a sterilised toothbrush, and then suspending it in 0.5mL Tris-EDTA for collection. Both samples were stored at −80°C until the time of processing. DNA was extracted from saliva and dental plaque by standard glass bead-based homogenisation and subsequent purification with a silica-membrane spin column using PowerSoil DNA Isolation Kit (Mo Bio Laboratories, Carlsbad, California, USA). DNA was eluted from the spin column with 30µL RNase-free water (Takara Bio, Inc., Shiga, Japan), and stored at −20°C after determining the amount and purity of DNA with a Nanodrop spectrophotometer (Thermo Fisher Scientific, Wilmington, Delaware, USA). Using DNA extracted from saliva or dental plaque as a template, a part of the V4 variable region of the bacterial 16S rRNA gene was amplified by two-step PCR. Tag-indexed PCR products thus obtained were subjected to multiplex amplicon sequencing using MiSeq System with MiSeq Sequencing Reagent Kit V.3 (Illumina) according to the manufacturer’s instructions. For the quality assurance, the minimum threshold of the total sequence reads for each sample was set to ten thousands, and the principal component analysis was used to eliminate outliers.

**Outcomes**

The following obstetric complications represented the primary outcomes. Gestational age was confirmed by measuring fetal crown rump length from 9 weeks to 13 weeks of gestation using transvaginal ultrasound. HDP was defined as gestational hypertension, pre-eclampsia, superimposed preeclampsia or chronic hypertension. Preterm birth was defined as spontaneous preterm labour, medically induced preterm labour or preterm premature rupture of membranes resulting in preterm birth at less than 37 weeks of gestation. GDM was diagnosed according to the International Association of the Diabetes and Pregnancy Study Groups criteria. The secondary outcomes were maternal body weight, blood pressure, physical activity, lifestyle changes, perinatal mental disorders, fetal growth, fetal movement and birth weight.

**Sample size calculation**

At this time, there is little reliable evidence to demonstrate how time-dependent trends of longitudinal dense data would differ by pregnancy outcomes. Therefore, a priori sample size calculation is not provided in the present study. However, considering that one of the main purposes of the MLOG study is to explore the relationship between patterns of longitudinal home blood pressure and the onset of HDP, we estimated a required sample size as follows. Based on the HDP incidence of approximately 10% at Tohoku University Hospital, with a statistical power of 90% and a significance level of 5%, a sample of 250 participants is required to detect a 5mm Hg difference in average home blood pressure (with a 7mm Hg SD) in the HDP group. To allow for 15% attrition and withdrawals during pregnancy, a minimum of 300 participants at baseline was required.

**Statistical analysis of longitudinal lifelog data**

One of the major advantages of the MLOG study is the dense information for each participant. Especially, time points for lifelog data collection are highly dense for each participant. For these datasets, per-person analysis of dynamic relationships between variables can be applied. Vector autoregressive modelling is a promising solution to find the predicates for each outcome. In addition, the Granger causality test can elucidate the temporal ordering of dynamic relationship between two or more variables and indicate putative causal associations. Some types of lifelog data were generated automatically; the others were manually input. We will first detect outlier data points, depending on the type of each lifelog, and eliminate them. The missing time-series lifelog data, ranging in 15%–33% of the total data points, would be imputed using the EM-imputation algorithm, for example, Amelia library, after normalising the data by data transformation if required. For downstream analysis, the data might be collapsed with time scale, for example, taking trimmed mean or median for each week, month or trimester.

**Statistical analysis of multiomics data**

The present study allows combination of longitudinal lifelog data with multiomics data. In contrast to single omics analysis, the multiomics analysis would reveal the complicated interactions between one and another. However, the sample size for multiomics analysis is usually relatively small. Dimension reduction via unsupervised or supervised learning for each omics data would be key ingredients to derive meaningful patterns from high dimensional data sets. Also, obtaining low dimensional representations provides a mean to deal with the multiple testing problem by decreasing number of statistical tests. For gene expression data, surrogate variable analysis and sparse factor analysis are frequently used to capture unknown batch effects in advance to expression quantitative trait locus (eQTL) analysis. The extracted factors can be removed from raw expression data to increase power for detecting associated genes. Several unsupervised clustering methods would be also applicable to obtain

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hidden patterns from dense time-course lifelog measurements, which might be related to pregnancy complications. Recently developed multiview factor analysis approaches have been used to integrate heterogeneous omics data to identify essential components to distinguish disease subtypes from few hundreds of samples. This line of approach would be a promising way to characterise biological status such as gestational age and to predict clinical outcomes such as spontaneous preterm birth.

Standard analyses would be also applicable for the selected variables and extracted factors (features). The association of outcomes with each feature will be analysed using statistical hypothesis tests such as Welch’s t-test, Fisher’s exact test, the χ² test and others as appropriate. Multiple logistic regression modelling will be used to adjust for confounders and to assess whether each feature or combination of features can be used to predict outcomes. Stepwise selection algorithms or regularised algorithms (eg, Least absolute shrinkage and selection operator (LASSO), ridge regression or elastic net) will be used to select the optimal number of contributing features that maximise the predictive power using the leave-1-out cross-validation or K-fold cross-validation methods.

Individual genetic features may have an effect on outcomes; therefore, some aggregated genetic risk score should be included in the prediction model. For example, SNVs, including rare variants in or around a chromosome region of a known or estimated risk gene, could be aggregated by considering their impacts on biological function of the gene or their minor allele frequencies in the population. However, this study is limited in the number of study participants, and the aggregated risk score might therefore contribute only slightly to the predictive power. To create a more reliable risk score, the estimates from other large-scale cohort data using polygenic score tools, for example, PRSice, could be used for this study.

**FINDINGS TO DATE**

**Clinical background**

A total of 302 women were enrolled, and the mean gestational weeks of recruitment was 16.4±4.9 weeks (mean±SD). A total of 285 participants have been followed up to delivery; their baseline clinical characteristics are described in table 1. The mean maternal age at delivery was 33.3±4.9 years. As for educational levels, 62% of the participants were high school graduates with or without vocational college education, and 21% had a college degree. The majority were employed (65%) in early pregnancy, and about 40% had a high household income (over 6 million yen per year). Approximately 42% of the participants were over 35 years of age, 51% were parous and 22% were overweight or obese by their prepregnancy BMIs (≥25 kg/m²). Overall, 8.4% of the participants had HDP, and 5.6% underwent spontaneous preterm birth. On average, infants were delivered at 38.0±2.3 weeks of gestation with a mean birth weight of 2907±572 g. The rate of low birth weight was 18%. Mean gestational weeks of the first and second blood sampling

| Table 1 Participant characteristics |
|-------------------------------------|
| Characteristics                  | Value |
| Maternal (n=285)                  |       |
| Age at delivery, years, mean (SD) | 33.3 (±4.9) |
| Age at delivery, years, n (%)     |       |
| 20–24                             | 12 (4.2) |
| 25–29                             | 45 (15.8) |
| 30–34                             | 107 (37.5) |
| 35–39                             | 90 (31.6) |
| 40–44                             | 30 (10.5) |
| 45–49                             | 1 (0.4) |
| Education (n=81), n (%)           |       |
| Elementary school/junior high school | 5 (6.2) |
| High school                       | 35 (43.2) |
| Vocational college                | 23 (28.4) |
| College degree and above          | 17 (21.0) |
| Others                            | 1 (1.2) |
| Data not available                | 204 |
| Occupation (n=270), n (%)         |       |
| Housewife or unemployed           | 93 (34.4) |
| Employed                          | 175 (64.8) |
| Student                           | 2 (0.7) |
| Annual household income, yen (n=248), n (%) |       |
| <2 million                        | 17 (6.9) |
| 2–4 million                       | 59 (23.8) |
| 4–6 million                       | 73 (29.4) |
| 6–8 million                       | 51 (20.6) |
| 8–10 million                      | 22 (8.9) |
| >10 million                       | 26 (10.5) |
| Parity, n (%)                     |       |
| 0                                 | 140 (49.1) |
| 1                                 | 93 (32.6) |
| ≥2                                | 52 (18.2) |
| Prepregnancy BMI*, kg/m², mean (SD) | 22.7 (±5.1) |
| Prepregnancy BMI, kg/m², n (%)    |       |
| <18.5                             | 36 (12.6) |
| 18.5–24.9                         | 186 (65.3) |
| 25.0–29.9                         | 34 (11.9) |
| ≥30.0                             | 29 (10.2) |
| Gestational weeks at delivery, mean (SD) | 38.0 (±2.3) |
| Mode of delivery, n (%)           |       |
| Non-caesarean                     | 179 (62.8) |
| Caesarean                         | 106 (37.2) |
| Pregnancy complication, n (%)     |       |
| Hypertensive disorder of pregnancy | 24 (8.4) |
| Spontaneous preterm birth         | 16 (5.6) |

Continued
The total number of collected data points as of June 2017 was calculated for the 285 final study participants. The approximate number of registered data points was 86,000 for body weight, 924,000 for home diastolic and systolic blood pressure, 86,000 for physical activity and 74,000 for body temperature. When physical conditions such as stool condition, severity of pain and fetal movement were combined, the total number of data points was over 6 million.

**Number of data points**

| Characteristics | Value |
|-----------------|-------|
| Neonatal (n=300) |       |
| Birth weight, g, mean (SD) | 2907 (±572) |
| Sex, n (%) |       |
| Male | 168 (56) |
| Female | 132 (44) |
| Low birth weight (<2500 g), n (%) | 54 (18) |

*BMI, body mass index.

**Data acquisition**

The percentage of data uploads as of June 2017 was calculated for the 285 final study participants. For each lifelog item, the upload rate for each participant was calculated from the total number of days of actual uploads divided by the number of days from enrolment to delivery. The mean upload rate for each lifelog item was 85.3% (physical activity), 82.1% (body weight), 80.4% (body temperature), 78.0% (morning home blood pressure), 71.6% (evening home blood pressure), 83.5% (sleep quality), 82.1% (condition of stool, severity of pain, severity of nausea, uterine contractions and palpitations) and 67.4% (fetal movement) (figure 3).

**Strengths and limitations**

Herein, we have described the rationale, design, objective, data collection methods and interim results of the MLOG study. The study was launched in September 2016, and baseline data collection ended in June 2017. A total of 285 participants uploaded lifelog data throughout pregnancy with a high data acquisition rate and over 6 million total data points. Biospecimens for multiomics analysis were satisfactorily collected and all tracked by LIMS.

There are three noteworthy features in the MLOG study. First, it is a prospective add-on cohort study based on TMM BirThree Cohort Study, with a full series of epidemiological data and a highly structured follow-up system for mothers, newborns and families. Second, we have successfully collected longitudinal, continuous, individual lifelog data with a high acquisition rate, which will enable us to assess dynamic changes in physiological conditions throughout pregnancy. Third, multiomics data will make it possible to fully understand the complex mechanisms of multifactorial pregnancy-related diseases and to overcome the unpredictability of these complications.
Prediction models using clinical and epidemiological information and circulating factors for pregnancy-related diseases have been developed extensively, and risk-assessment approaches using clinical information have also been developed. However, there is a lack of evidence for the benefits of these predictive models for routine clinical use. Once the likelihood of a pregnancy-related disorder is estimated with high sensitivity and specificity, evidence-based clinical interventions could reduce the rate of maternal and neonatal morbidity and mortality. Therefore, an early-prediction algorithm that can be used with a high level of confidence is needed to obtain better outcomes for patients with pregnancy complications.

Recently, several studies of sample sizes comparable with ours exploiting lifelog or multiomics data were reported. One of the studies analysed lifelog and multiomics data, collected from 108 individuals at three time points during a 9-month period. In their study, several remarkable relationships were identified among physiological and multiomics data through integrated analyses. Another study investigated genome-wide associations between genetic variants and gene expression levels across 44 human tissues from a few hundreds of postmortem donors. They studied both cis-eQTL (within 1 Mb of target-gene transcription start sites) and trans-eQTLs (more distant from target genes or on other chromosomes) with 350 whole blood samples and thereby identified 5862 cis-eQTL and one trans-eQTL associations. These previous studies indicate that our time-course high-resolution reference catalogue with 285 pregnant women would be well applicable to high-dimensional data analyses such as searches for quantitative trait loci and molecular risk markers.

Potential limitation of the present study is participant recruitment only at Tohoku University Hospital that is one of the tertiary hospitals in Miyagi Prefecture for high-risk populations. Therefore, the sample size is limited, and the results might not be applicable to the general populations. Inclusion criteria of the present study limited the eligibility to pregnant women with age >20 years and the ability to access the internet using a smartphone. Therefore, results might not be applicable to the general populations. Therefore, the sample size is limited, and the results might not be applicable to the general populations.

Hopefully, our study will result in the development of a novel stratification model for pregnancy-related diseases employing multiomics and lifelog data.

The MLOG study will enable us to construct a time-course high-resolution reference catalogue of wellness and multiomics data from pregnant women and thereby develop a personalised predictive model for pregnancy complications. Progressive data sharing and collaborative studies would make it possible to establish a standardised early-prediction method through large clinical trials.

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