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The identification of early predictors of pregnancy complications through wearable technologies in a Brazilian multicenter cohort: Maternal Actigraphy Exploratory Study I (MAES-I)

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Keywords:	wearable technologies, actigraph, physical activity, sleep patterns, pregnancy complications

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STUDY PROTOCOL

The identification of early predictors of pregnancy complications through wearable technologies in a Brazilian multicenter cohort: Maternal Actigraphy Exploratory Study I (MAES-I)

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Abstract

Introduction: non-invasive tool capable of identifying predictors of maternal complications would be a step forward on the improvement of maternal and perinatal health. There is association between modification of physical activity (PA) and sleep-wake patterns and the occurrence of inflammatory, metabolic, pathologic conditions as chronic diseases. The actigraph device is validated to estimate PA and sleep-wake patterns and might be valuable to identify predictors for maternal complications, widening the window of opportunity to prevent, diagnose or treat specific conditions prior to the development of typical symptoms or clinical signs, assessing PA and sleep-wake patterns during pregnancy.

Methods and analysis: A cohort will be held in 5 centres from the Brazilian Network for Studies on Reproductive and Perinatal Health. MAES-I will enroll 400 low-risk nulliparous women that will wear the actigraph device on the wrist during day and night (24h/day) uninterruptedly from 19-21 weeks until childbirth. Changes in PA and sleep-wake patterns through pregnancy will be analyzed, considering gestational age ranges, in women with and without maternal complications during pregnancy, such as preeclampsia, preterm birth (spontaneous and provider-initiated), gestational diabetes, maternal haemorrhage and also perinatal outcomes. A predictive model for screening pregnant women for risk of specific adverse maternal and perinatal outcomes is planned to be then developed using the actigraphy data.

Ethics and Dissemination: MAES-I study has been reviewed and approved by each Institutional Review Board (IRB) and also by the National Council for Ethics in Research. Detailed information of the study is provided in the Brazilian Cohort website (www.medscinet.com/samba) and findings will be publicized in scientific literature and Institutional webpages.

Discussion: Multiple benefits might arise from the development of a predictive tool for maternal complications during pregnancy, providing a new concept for antenatal care monitoring programmes.

Keywords: wearable technologies; actigraph; physical activity; sleep patterns; sleep-wake cycle; prediction; pregnancy complications.

Strengths and limitations of this study

- This multicentre cohort will collect comprehensive data on the main maternal and perinatal complications as pre-eclampsia, small for gestational age/fetal growth restriction, preterm birth and gestational diabetes mellitus.
- Physical activity and sleep patterns will be estimated through an innovative wearable device used in the natural environment of the study subject.
- Physical activity and sleep patterns will be estimated from the beginning of the second half of pregnancy until delivery, covering a wide interval during pregnancy and enabling the study of PA and sleep patterns changes throughout pregnancy.
- One possible limitation refers to the uncovered first half of pregnancy regarding this information.

Background

Reducing the global maternal mortality ratio to less than 70 per 100,000 live births by 2030 is one of the targets of the new United Nations Sustainable Development Goals [1]. Multiple challenges need to be tackled to achieve this target, but the 2016-2030 health and development agenda goes well beyond mortality reduction. The Global Strategy for Women's, Children's and Adolescent's Health aims to ensure that every newborn, women and child not only survive but thrive. This will only be possible if a transformative agenda, with innovation at the central stage, is put into action [2].

One of the major challenges that need to be addressed is optimizing the recognition of early predictors and identifiers of maternal and perinatal complications. Delays in diagnosing and managing maternal complications have been associated with poor outcomes [3]. The reduced self-perception of clinical signs related to maternal complications, difficulties in accessing the health system and poor quality of care may contribute to the late identification of complications and worsened prognosis. The development of a non-invasive Antenatal Care (ANC) tool capable of identifying maternal sub-clinical signs during pregnancy may provide the window of opportunity for early identification of abnormal patterns of physiologic parameters related to pregnancy complications and enable their prevention or early treatment. Shortening the time between the onset of a complication and the initiation of the appropriate management allow for secondary prevention and reduction of maternal morbidity and mortality [3–7].

Pervasive computing (i.e. the trend towards embedding microprocessors in everyday-life objects so they can generate data) and wearable technology (i.e. clothing and accessories incorporating computer and advanced electronic technologies such as wrist and/or waistband sensors) are ubiquitous and able to generate a new dataset that needs to be correlated with pregnancy outcomes. Preterm birth and preeclampsia, for instance, are two important pregnancy complications that have a relatively long subclinical phase before the appearance of signs or symptoms [8,9]. It is plausible that during this subclinical phase of certain conditions the pattern of physical activity (PA) or sleep-wake rhythm is affected in some way and this change could be captured through wearable devices. Although some studies show that PA patterns and

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3 circadian rhythm abnormalities (actigraphy) may be related to systemic inflammation
4 and diseases in the general population [10,11], published literature correlating
5 wearable technology data and maternal complications are very scarce.
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8 The human circadian rhythm is ruled by endogenous physiologic mechanisms and
9 environmental stimuli [12]. There is solid evidence showing that modification of
10 circadian rhythm or sleep and PA patterns are an underlying condition related to
11 inflammatory, degenerative and/or metabolic chronic diseases as diabetes,
12 hypertension, and cancer [13]. Circadian misalignment is defined as having
13 inappropriate timed sleep and wake, misplaced feeding periods and modification of
14 activity behavior.
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21 The determination of cause or consequence effect between these modifications and
22 the development of pathological conditions is a complex task. It seems that changes in
23 appetite-stimulating hormones, glucose metabolism, inflammatory markers, and mood
24 are some of the related pathways [13–15]. Leproult *et al.* evaluated the effect of
25 circadian misalignment on metabolic and inflammation markers in cardiovascular
26 disease [15]. The insulin action and release, and also the levels of some inflammatory
27 markers that are predictors for cardiovascular diseases, were abnormal in individuals
28 with circadian misalignment. The mechanisms involved in the association between
29 changes of PA pattern and pathologic conditions seem to be of multiple etiologies. Sani
30 *et al.* assessed the circadian rhythm of more than 2,300 African descendant adults. More
31 than evaluating physical activity itself, the authors aimed to identify chronobiologic
32 patterns of adults from different socioeconomic settings. The study identified that
33 chronobiologic behavior can vary depending on individual BMI, socioeconomic
34 background, work type and time of sunlight exposure. Possibly, many other factors are
35 involved in modifications of chronobiologic behavior, such as pathologic conditions.
36 Some metabolic, cognitive, cardiovascular and other chronic degenerative diseases
37 have been associated with particular patterns of PA and sleep [10,11,16–18]. A
38 previous observational study assessed various sleep parameters during pregnancy, e.g.
39 sleep onset latency (SOL), wake after sleep onset (WASO) and total nocturnal sleep
40 time (TST). Difficulty in initiating sleep in early pregnancy was associated with higher
41 body mass index, greater weight gain and higher blood pressure during pregnancy
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3 [17]. Palagini *et al.* reviewed clinical evidence between chronic sleep loss and
4 pregnancy adverse outcomes, discussing common mechanisms of stress system
5 activation [19]. Low-quality evidence suggests an association between sleep loss and
6 prenatal depression, gestational diabetes, preeclampsia, abnormal length of labour,
7 caesarean delivery, abnormal fetal growth, and preterm birth. Those results
8 corroborate with other findings regarding pregnancy and sleep disorders [20–23].
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13 The assessment of PA and the sleep patterns can be performed using small wrist (or
14 waist) devices similar to a regular watch (actigraphy technology). The type of sensor,
15 batteries, materials and output data have been substantially developed in recent
16 years, enabling low cost, comfort, discretion and performance [24]. Nowadays there
17 are devices that are portable, lightweight and with a large capacity to storage
18 information, including a software with automatic scoring algorithms packages for the
19 detection of wakefulness, sleep periods and PA [24,25]. The actigraphy estimation of
20 PA and sleep patterns is validated as a proxy for chronobiologic behavior [26–29] and 7
21 to 14 days using the actigraph device provides reliable estimates of PA behavior in
22 older adults [30–32]. Both hip and wrist devices show reliable and acceptable
23 performance in estimating PA and sleep-wake patterns [33–36].
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33 The main advantages of using wearable devices for actigraphy is the non-invasiveness,
34 24/7 monitoring of the circadian pattern and PA, and informing sleep habits and
35 parameters in the user natural environment [24,25,28]. We propose an innovative and
36 strategic approach to monitor PA and sleep-wake patterns during pregnancy,
37 establishing a large database comprised of clinical, epidemiological, PA and sleep-wake
38 variables potentially capable of composing a prediction model for maternal
39 complications during pregnancy. The main goal of this study is to identify early
40 predictors of pregnancy complications by correlating data generated on PA and sleep
41 patterns through wearable devices (wristband sensors) with maternal and perinatal
42 complications and outcomes.
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50 **Methods/Design**

51 ***Study design***

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3 We will conduct a cohort study of 400 low-risk pregnant women using wrist sensor
4 bands able to capture information on daily physical activity and sleep patterns
5 (exposure). This cohort study will be implemented in 5 ANC clinics linked to obstetric
6 units in 3 different regions of Brazil that are already part of the Brazilian Network for
7 Studies on Reproductive and Perinatal Health [37], as shown in Table 1. During a
8 period of eight months, the ANC clinics will identify eligible cases for using the
9 wristband sensors. Wearable technology data will be correlated with the occurrence
10 of pregnancy and childbirth complications and outcomes, thus understood as an
11 effect.
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18 Eligible women will be identified up to 21 weeks of gestation and invited to participate.
19 A proper consent form will be applied and the women who agree to participate will
20 receive a wristband sensor to be used starting at 19-21 weeks until childbirth,
21 uninterruptedly.
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26 ***Study setting and population***

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28 Brazil is a multi-ethnic mixed-race population of diverse resourced settings [38].
29 Despite the considered high global overall human development index (HDI 0.727) in
30 2010, the HDI of Brazilian municipalities ranged from 0,862 to 0,418 [39]. The
31 possibility of considering such mixed population is suitable to explore information
32 regarding maternal patterns of mobility and sleep, maximizing external validity and
33 comparisons to other populations. A few reasons might support the study population
34 focused in low-risk nulliparous women: 1) Previous obstetric history can refer to
35 known risk factors for many maternal complications such as preterm birth,
36 preeclampsia, and diabetes [13,40]. Nulliparous women enable unbiased sampling
37 regarding obstetric history. 2) Women with previous morbidity such as hypertension,
38 diabetes, nephropathy or others chronic/degenerative diseases are more likely to
39 present abnormalities of sleep-wake rhythm or physical activity patterns during
40 pregnancy.
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51 ***Sampling***

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53 The five participating centers are regional referral obstetric units responsible for
54 antenatal care assistance mainly for high-risk pregnant women. Participating centers
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3 are listed in Table 1. Nevertheless, there are primary health care units strategically
4 linked with these participating centers, enabling the identification and enrollment of
5 low-risk pregnant women. The recruitment strategies include approaching all eligible
6 women in these participating centers and their linked facilities. An informed consent
7 form will be applied for women who agree to participate.
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10 11 12 *Eligible women: Low-risk pregnant subjects*

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14 There is no international consensus on the criteria for low-risk pregnancies, although
15 there are several known factors associated with maternal and perinatal adverse
16 outcomes. A recent study evaluating complications of “low-risk” pregnancies of US
17 Americans (10 million births from 2011 through 2013) showed that 29% of low-risk
18 women had an unexpected complication requiring no routine obstetric/neonatal care
19 [41]. This shows the difficulty in establishing a “low-risk profile” for maternal/perinatal
20 complications. As an exploratory study, we will exclude potential known confounders
21 of pre-pregnancy conditions related to adverse maternal or perinatal outcomes as
22 shown in Table 2, in order to assess PA and sleep patterns of a mostly “normal”
23 population. Lifestyle habits and body composition (Body mass index, height, etc.)
24 characteristics, and some non-severe chronic diseases as thyroid disorders, non-severe
25 anaemia and/or asthma are not among exclusion criteria but may be part of subgroup
26 analyses (composition of any previous disorder, e.g.). Intra and inter-individual
27 analyses of PA and sleep patterns enable the identification of potential confounders
28 affecting primary outcomes, avoiding potential biases.
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32 Eligible women will be enrolled between 04-21 weeks. The inclusion and exclusion
33 criteria are presented in Table 2.
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36 37 38 ***Data collection methods***

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40 Essentially, MAES I study is comprised of 4 key set points – 3 clinical visits during
41 pregnancy and a postnatal visit. The clinical visits will be held at 1) between 19-21
42 weeks; 2) between 27-29 weeks; 3) between 37-39 weeks. At first, second, third and
43 postnatal visits, additional information regarding maternal history, details on
44 pregnancy complications, maternal biophysical data (weight, height, skinfolds) and
45 pregnancy adverse outcomes will be collected following a specific Standard Operating
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3 Procedure (SOP) specially developed for MAES-I study. Additionally, the Perceived
4 Stress Scale [42] and Resilience Scale [43] will be applied during 27-29w visit. Figure 1
5 shows the set points of MAES-I study.
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8 Eligible women will be invited to use a small wrist device similar to a regular watch
9 (GENEActiv Original – Activinsights®). The device contains sensors that estimate PA and
10 sleep-awake patterns through a proper software algorithm. At the first set point of
11 MAES-I study (between 19+0 - 21+0 weeks of gestation), eligible women who agreed
12 to participate will start using the wrist bracelet device on the non-dominant arm
13 during day and night (24h/day) uninterruptedly until childbirth (including bathing or
14 aquatic activities). The acquisition of actigraphy data can be performed in different
15 frequencies (from 10Hz to 100Hz). Since the frequency of data acquisition impacts on
16 the battery life of the device (inverse relationship), the measurement frequency will be
17 set up according to the participant's gestational age (Table 3). This information will be
18 registered in the database accordingly. The data accumulated will be downloaded
19 during participant's antenatal care visits, according to the maximum return periods
20 showed in Table 3. The maximum return periods were calculated taking into
21 consideration the expected battery life.
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33 A leaflet with detailed information and FAQ (Frequently asked questions) on the device
34 will also be provided to the women. They will also have a cell phone number to call
35 whether doubts arise regarding the procedures for using the device, or if any technical
36 or medical concern arises.
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40 All actigraphy data collected will be entered into proper software to interpret data and
41 generate an output file. Then, the actigraphy data will be uploaded to an online
42 database platform developed by MedSciNet®, where all clinical data of the study will
43 also be registered. The actigraphy software uses several algorithms to estimate
44 physical activity and sleep patterns. The database is centralized, secure, internet-
45 based and allows several procedures for prospective and retrospective monitoring,
46 hierarchical access (local user, general manager, etc.). The database will be translated
47 into Portuguese and English, facilitating data collection for Portuguese-speaking team
48 and international monitoring. A correspondent paper form will be available for data
49 collection if necessary (e.g. internet connection failure for instance).
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Decision to start monitoring PA and sleep patterns between 19-21weeks

There are various underlying mechanisms involved in the development of the maternal and perinatal adverse outcomes that will be assessed, as preterm birth, preeclampsia, gestational diabetes, fetal growth restriction and small for gestational age. The pre-clinical phase, stage where there are no clinical signs or symptoms, might be different for each disease and dependent on environmental and individual aspects. The study of adverse maternal and perinatal predictors has been focused in early pregnancy so far (first trimester), aiming to maximize the window of opportunity for preventative interventions. However, we hypothesized that the modification of PA and/or sleep pattern due to maternal underlying changes of biological function might not be evident at a very early stage in pregnancy before the beginning of the pre-clinical phase. Our hypothesis is that it possibly occurs shortly before symptoms.

Additionally, to establish the period between 19-21 weeks as appropriate to start the assessment of PA and sleep patterns taking into consideration that the prevalence of the main maternal complications, as preeclampsia, fetal growth restriction, and preterm birth, are more common in late pregnancy. A recent cross-sectional study conducted in 20 referral centres in Brazil, including the five participating centres of this proposal, showed that the occurrence of preterm birth before 28 weeks comprised less than 1% of all births and less than 8% of all preterm births [44]. In addition, the early onset of preeclampsia (before 34 weeks of gestation) complicates less than 0.4% of all pregnancies, according to a large retrospective cohort of more than 450,000 deliveries in USA [45]. Figure 2 outlines the predicted prevalence of preterm birth and preeclampsia in the second trimester, highlighting its clinical presentation through pregnancy in red. Our hypothesis is that PA and sleep patterns might be altered closely to the clinical presentation, still in preclinical phase. Thus, the start of assessment between 19-21 weeks seems to be very reasonable, providing a wide interval to monitor and predict the main maternal and perinatal adverse outcomes.

Actigraph device

The actigraph device that will be used to monitor PA and sleep-wake patterns is GENEActiv Original (GENEActiv, Activinsights Ltd, Huntingdon, UK). The device has multiple sensors as microelectromechanical (MEMS) accelerometer, temperature

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3 (linear active thermistor) and light (silicon photodiode), providing crude raw data for a
4 variety of applications.
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6 *Wrist vs waist wear: advantages and performance*

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8 Wrist wear of actigraph devices provides more comfortable use during wake and sleep
9 periods and highest wear time compared to waist monitors [33,46]. A non-systematic
10 review published in 2011 showed that actigraphy is a useful and reliable tool to assess
11 sleep patterns and circadian rhythm disorders, although there are some limitations on
12 diagnosing sleep diseases or measuring sleep stages [25]. Actigraphy showed excellent
13 concordance with polysomnography in assessing sleep parameters in healthy subjects
14 (sensitivity >90% in estimating total sleep time, for instance). A recent study evaluated
15 the concordance of physical activity estimation of wrist device in free-living settings in
16 forty overweight or obese women [34]. They used both wrist and hip devices, and a
17 small camera that captured participant behaviour for 7 days, enabling the monitoring
18 of physical activity behaviour (gold-standard comparison). The hip and wrist machine
19 learning (ML) classifiers used are different due to the different methods/algorithms to
20 estimate physical activity [34]. The sensitivity and specificity of hip and wrist
21 estimations according to Ellis *et al* are showed in Table 4 [34].
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33 Two years ago, the same author had published a similar evaluation using 40 adults
34 (women and men), showing that the hip and wrist accelerometers obtained an average
35 accuracy of 92.3% and 87.5%, respectively, in predicting PA types [47].
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39 Staudenmayer *et al* developed an investigation with 20 participants also using two
40 devices (wrist- and hip- worn), and showed that wrist actigraphy can estimate energy
41 expenditure accurately and relatively precisely [48]. Another study evaluating PA
42 patterns in a free-living environment with wrist devices showed that women in the top
43 40% or bottom 40% of the distribution of daily PA, hip and wrist accelerometers
44 agreed on the classification for about 75% of the women [49]. Additionally, the total
45 activity (counts per day) was moderately correlated (Spearman's $r = 0.73$) between the
46 wrist and hip worn devices.
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53 At the best of our knowledge, there are no systematic reviews or other high-quality
54 evidence-based recommendation supporting a particular method. Although wrist wear
55 of actigraphy is more conventional and accurate, it might not be the best choice for
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3 assessing long periods of PA or sleep patterns, even more considering the similar
4 performance of the wrist wear. The current proposal does not intend to diagnose
5 pathologic behaviours or diseases, but to identify different patterns along pregnancy
6 and in different subgroups of women. Therefore, supported by the evidence that wrist
7 wear of actigraphy devices can accurately and more comfortably estimate PA and
8 sleep patterns, mainly for long periods and in the free-living environment, the MAES-I
9 study group adopted wrist wear devices.
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15 **Main variables**

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17 The independent variables assessed as potential predictors of maternal complications
18 will be related to sleep-wake cycle and mobility as:
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21 *“Sleep” variables*

- 22 - Sleep onset latency (SOT): time elapsed between full wakefulness to sleep.
- 23 - Total sleep time (TST): The amount of actual sleep time in a sleep episode
24 (excludes awakes).
- 25 - Wake after sleep onset (WASO): defined as total amount of time awake after sleep.
- 26 - Sleep Efficiency (SE): the proportion of sleep in the period potentially filled by
27 sleep-ratio of total sleep time to time in bed.
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34 The actigraph device collects many pieces of information related to body position and
35 body movements to estimate the described sleep variables. Then, actigraphy software
36 will be used to analyse the data and generates the output variables.
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40 *“Physical activity” variables*

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42 Actigraphy technology estimates physical activity through various parameters
43 collected by the actigraph device. Briefly, according to Freedson *et al*, the triaxial
44 sensors stressed by acceleration forces can estimate the intensity of movements. The
45 acceleration signal is converted to digital signal and summed over a user specified
46 time interval (epoch). At the end of each epoch the activity count is stored. Then,
47 according to Count per minute (CPM) cut points, the PA intensity can be categorized
48 [50]. The information is translated by the software using proper algorithms into
49 quantitative variables as following:
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- 3 - Sedentary time (hours/day): the number of hours per day of count per minute
- 4 between 0-99.
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- 7 - Light activity (hours/day): the number of hours per day having count per minute
- 8 between 100 - 1951.
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- 11 - Moderate activity (minutes/day): the number of hours per day having count per
- 12 minute between 1952 - 5724.
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- 14
- 15 - Vigorous activity (minutes/day): the number of hours per day having count per
- 16 minute between 5725 - 9498.
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- 19 - Very vigorous activity (minutes/day): the number of hours per day having count
- 20 per minute between 9499 - ∞ .
- 21
- 22
- 23 - MET rates: Metabolic Equivalent (METs) are commonly used to also express
- 24 the intensity of physical activities. One MET is the energy cost of resting quietly,
- 25 often defined in terms of oxygen uptake as $3.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. MET rate
- 26 expresses a person's working metabolic rate relative to their resting metabolic
- 27 rate. Briefly, the triaxial piezoelectric sensors stressed by acceleration forces can
- 28 estimate the intensity of movements, converted to the oxygen consumption
- 29 required to perform such movement.
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- 35 - Step counts/day: estimated steps count per day.
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37 *Outcomes*

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39 The primary outcomes are late pregnancy complications as:

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- 41 - Preeclampsia: Hypertension after 20 weeks of gestation, systolic BP $\geq 140\text{mmHg}$
- 42 and/or diastolic BP $\geq 90\text{mmHg}$ (Korotkoff V) on at least 2 occasions 4h apart with:
- 43 1) Proteinuria 300 mg/24h or spot urine protein: creatinine ratio $30 \text{ mg}/\text{mmol}$
- 44 creatinine or urine dipstick protein $\geq (+)$ OR, in the absence of proteinuria,
- 45 hypertension and 2) any multi-system complication that are: Haematological
- 46 abnormalities; thrombocytopenia (platelets $< 100 \times 10^9/\text{L}$); disseminated
- 47 intravascular coagulation (DIC), and haemolysis; Liver disease: increased
- 48 aspartate transaminase and/or alanine transaminase $> 45 \text{ IU}/\text{L}$ and/or severe
- 49 right upper quadrant or epigastric pain, liver rupture; Neurological problems:
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eclampsia, imminent eclampsia (severe headache with hyperreflexia and persistent visual disturbance), cerebral haemorrhage; Acute renal insufficiency: new increase in serum creatinine to > 100 mmol/L antepartum or > 130 mmol/L postpartum; Pulmonary oedema confirmed by chest x-ray [51].

- Gestational Diabetes: new diabetes developing in pregnancy according to the WHO recommendation [52] that defines gestational diabetes as having:
 - o Fasting plasma glucose \geq 92 mg/dl, or
 - o 1-h plasma glucose tolerance test (75g load) \geq 180 mg/dl, or
 - o 2-h plasma glucose tolerance test (75g load) \geq 153 mg/dl.
- Spontaneous Preterm Birth: spontaneous onset of preterm labour or premature rupture of membranes leading to preterm birth, childbirth before 37 weeks of gestation.
- Provider-Initiated Preterm Birth: defined as childbirth occurring at less than 37 weeks, medically indicated due to maternal/fetal compromise or both;
- Maternal Hemorrhage: Classified in 1) Antepartum haemorrhage defined as bleeding from the genital tract after 24 weeks of gestation; 2) Primary Postpartum haemorrhage as the loss of 500 ml blood or more from the genital tract within 24 hours of the childbirth.

Secondary outcomes include childbirth variables and neonatal adverse outcomes as fetal death, caesarean section, small for gestational age (defined as birth weight below percentile 10 for gestational age), Apgar score < 7 at 5 minutes, neonatal severe morbidity (Table 5) and neonatal mortality before discharge.

Plans for analyses

Sample size estimation

This is an exploratory and innovative study focused on a specific population (pregnant women) and therefore there are no previously published parameters available for sample size estimation. Considering a relatively wide range of frequency of complications arising in pregnancy from 3 to 20% (including preeclampsia, fetal growth restriction, gestational diabetes, hemorrhage, preterm birth, etc.), a theoretical large population size (above 1 million pregnant women), an acceptable margin of error of 4%, the involvement of 5 clusters (participating centers) and a 95% level of confidence,

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3 384 women would be necessary. Therefore, we are rounding up this estimation for at
4 least 400 initially low-risk pregnant women to be enrolled in the study. We estimated
5 the incidence of some main maternal complications considering the following studies:
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- 8 - Pre-eclampsia: An international prospective cohort study with nulliparous women
9 called SCOPE used similar criteria for the low-risk profile, having 5% of incidence of
10 pre-eclampsia [53].
- 11 - Preterm Birth: A recent cross-sectional study conducted in 20 referral obstetric
12 centres in Brazil, including the five participant centres of this proposal, showed a
13 prevalence of 12.3% of all births [44].
- 14 - Gestational Diabetes: SCOPE international cohort, previously mentioned, had a
15 prevalence of 8.9% of gestational diabetes in low-risk screened nulliparous women,
16 according to mainly to the NICE guidelines [54].
- 17 - Fetal growth restriction/small for gestational age: SCOPE international cohort,
18 previously mentioned, had a prevalence of 10.7% of newborns small for gestational
19 age, according to the customized centiles of birthweight (<10%)[55].
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29 *Analyzes and statistics details*

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31 According to these studies, the predicted incidence of these complications, the leading
32 causes of maternal and perinatal adverse outcomes, seems adequate for the current
33 proposal and sample size estimation, although the complications are not cumulative.
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37 Firstly, we will identify PA and sleep-wake patterns of women who did not develop
38 adverse maternal or perinatal outcomes. It will permit the recognition of a normal PA
39 and sleep-wake patterns in low-risk population without complication during
40 pregnancy. Using the same population, we will analyze changes in PA and sleep-wake
41 patterns through pregnancy, allowing for gestational age periods.
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46 Then, we will compare the PA and sleep-wake patterns of women who developed
47 specific adverse maternal or perinatal outcomes with those who did not. The
48 differences between groups might be identified to be used as potential markers for
49 specific pregnancy complications.
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54 After that, we will analyze changes in PA and sleep-wake patterns of women who
55 developed adverse maternal or perinatal outcomes through pregnancy, comparing the
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3 patterns before with those after the onset of maternal complications, trying to
4 discover which changes might be related to pregnancy complications.
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7 Finally, we will develop a predictive model for screening pregnant women for risk of
8 specific adverse maternal and perinatal outcomes using PA and sleep-wake data
9 estimated with actigraphy technology.
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12 The analysis will be performed using the actigraph software that translates the
13 collected information into PA and sleep-wake parameters. Additionally, Friedman and
14 Wilcoxon for paired samples, t-test, and ANOVA for repeated measures will be applied
15 to achieve statistical analyses.
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19 ***Discontinuation of participants***

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21 The criteria for discontinuation include:
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- 23 - Withdrawal of consent;
- 24 - Not regularly using the actigraph device for long periods, above 50% of all planned
25 time. The information that they are not using the device properly will be recorded
26 if women notice the MAES-I team. Otherwise, the low use of the device will be
27 noticed after data discharge during antenatal care visits.
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31 - The loss to follow-up, not allowing the download of actigraphy data.
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35 ***Data and Sample Quality***

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37 All entered data will be prospectively and retrospectively monitored by local research
38 assistants and a global monitor. Internal consistency of variables will be constantly
39 performed by the database and error messages are automatically flagged. A local
40 research assistant will be responsible for checking all forms and actigraphy data before
41 locking forms, assuring good quality of data. Then, the local principal investigator (PI)
42 will be responsible for signing the case, enabling its incorporation to the final database.
43
44 The University of Campinas will coordinate, implement and monitor the study in the
45 five participating centres. A general manager and a global monitor are also part of the
46 team of the coordinating centre. The local team of each participating centre is
47 comprised of a Local PI and research assistants.
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54 ***Ethical aspects***

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3 MAES-I study focuses on low-risk nulliparous Brazilian pregnant women. Despite being
4 considered of low risk for maternal and perinatal complications, they are not free of
5 suffering complications. Furthermore, the first and second delays, defined as a delay in
6 deciding to seek care and delay in reaching a health care facility [56], are not
7 uncommon, establishing a barrier between early recognition of symptoms and timely
8 interventions capable to successfully treat potentially life-threatening conditions. We
9 believe that women will feel encouraged, empowered and willing to participate in the
10 study that aims to develop a potentially useful prenatal care tool to identify the risk for
11 maternal and perinatal morbidity and mortality. Following national ethical regulations,
12 the participants will not receive any financial compensation.
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20 Women who agree to participate in the study will not have any disadvantages or injury
21 of their prenatal care. On the contrary, they will receive a telephone number to
22 contact the clinical researchers at any time (24/7 service), which enables a closer
23 contact with researchers and providers of care, since the MAES-I team are committed
24 to contacting providers of care if any potential complication is noticed by participants.
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29 The participating women will not be responsible if loss, theft or damage to the wrist
30 device occurs. However, they will be asked to return the device after they finished the
31 participation in the study, in order to use it for new women entering the study. No self-
32 damage is expected in those who use the device. The identity of all women will be kept
33 confidential.
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38 Participating women will not be able to identify any PA or sleep parameters at any
39 stage of the study. The download of the data is only possible through the own licensed
40 software of the device.
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44 MAES-I study has been reviewed and approved by the National Committee for Ethics in
45 Research of Brazil (CONEP) and by the Institutional Review Board (IRB) of the
46 coordinating centre (Letter of approval 1.834.116 issued on 24th November 2016) and
47 of all other Brazilian participating centres. All women who will be enrolled in the
48 MAES-I cohort will sign an informed consent form.
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53 The ethical principles stated in the Brazilian National Health Council (Resolution CNS
54 466/12) will be respected in every stage of this study. The anonymity of the source of
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3 information will be guaranteed and the care for the women will be provided
4 independently of her agreement to participate in the study. The study also complies
5 with the Declaration of Helsinki amended in Hong Kong in 1989. The methodological
6 and ethical aspects of MAES-I study protocol were developed following STROBE
7 guidelines [57].
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10 11 *Patient and Public Involvement*

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14 Patients and public were not involved in this study for the development of the
15 research question and outcome measures. However, the choice for a wrist device was
16 based on the preference of users as reported. Participants of the study will have access
17 to the results by its webpage that will open access.
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23 **Discussion**

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26 The actigraphy is an innovative, non-invasive, non-operator dependent, wearable
27 technology, which enables the estimative under real life conditions of diverse variables
28 related to mobility, physical activity, sleep-wake, and circadian cycle patterns.
29 Actigraph devices show high sensitivity in sleep-wake parameters detection and are
30 currently highly recommended by the American Sleep Disorder Association for
31 diagnosis and therapy response of circadian rhythm disorders [27,28,58]. Although
32 some studies show that 7 to 14 days using the actigraph device provides reliable
33 estimates of physical activity behavior in older adult, it is not absolutely clear how
34 many days is needed to estimate habitual PA by using the wrist/waist device during
35 pregnancy. In general, it seems to depend mainly on the type of actigraph device,
36 position of wear and target population [30,33]. Nevertheless, MAES-I study will
37 provide sufficient data to assess different patterns along pregnancy.
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47 The use of wearable physical activity monitors has grown enormously due to the
48 interest about the relationship between the pathophysiology of diseases and physical
49 activity and sleep patterns. A recent study on the use of physical activity monitors in
50 human physiology research unravels the current and potential uses of actigraph device
51 as in strategies to promote healthier behaviour or to predict outcomes [59]. The
52 authors conclude that physical activity monitors, as others new 21st century
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3 technologies, have already transformed physiology research, revolutionizing the way
4 we assess patients and opening new areas of interest. In addition, the use of objective
5 measures to evaluate habitual sleep duration and outcomes in pregnancy is critical,
6 taking into account recent investigations reporting little agreement between objective
7 and subjective assessments of sleep time [60].
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11 Alterations in sleep patterns, as less deep sleep and more nocturnal awakenings, can
12 be observed in pregnancy as early as 10-12 weeks gestation [61]. Sleep disturbances
13 during pregnancy have been associated with preterm delivery, gestational
14 hypertensive disorders, glucose intolerance and increased risk of caesarean delivery
15 [24]. Shorter night time sleep was also associated with hyperglycemia [60]. Persistent
16 sleep deficiency is correlated with depressive symptoms and stress perception by
17 pregnant women [61]. These studies lay correlation between PA patterns and sleep
18 disturbances determining complications, in a well-established relationship of cause and
19 consequence, although sometimes it could not be adequately determined due to the
20 study design [17].
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24 In a distinct way, our analysis intends to figure out if the maternal complication could
25 be identified by physical activity and/or sleep patterns modifications, even during its
26 pre-clinical period, previous the appearance of clinical signs. Considering the existing
27 evidence, we speculate that the PA and/or sleep patterns change days or weeks before
28 the clinical presentation of the complication. In general, the signs and symptoms of
29 some maternal outcomes are part of the gold-standard criteria for diagnosis (high
30 blood pressure, proteinuria and/or edema in the case of preeclampsia; premature
31 contractions and cervical ripening/dilation in preterm birth; abnormal placental blood
32 flow and insufficient fetal growth in Intrauterine Growth Restriction).
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36 Then, the use of actigraph device during prenatal visits has a potential to become a
37 new tool to monitor pregnant women, improving maternal health care, identifying
38 altered PA and/or sleep patterns, measured objectively through actigraphy, before the
39 occurrence of those signs and symptoms. Therefore, the focus would be offering new
40 technology to monitor the development of a potential maternal complication. Other
41 positive points of our study are the period of data collection (from 19 weeks till
42 delivery) and the low-risk profile of the cohort. Through which, it would be possible to
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3 describe a PA and sleep patterns in a low-risk pregnant population and better interpret
4 actigraphy data among pregnant women. The current clinical and biological predictors
5 for the main maternal complications as preeclampsia, preterm birth, maternal
6 haemorrhage, and gestational diabetes still lack for effective sensitivity and specificity.
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10 If this is confirmed to be true, an important step will be achieved for a possible
11 introduction of screening non-invasive procedures during prenatal care with the
12 purpose of identifying women at higher risk of developing those conditions. Therefore,
13 they could receive specific orientation on prevention and earlier detection of the onset
14 of condition for taking immediate action to look for professional health care and
15 receiving appropriate interventions, avoiding delays that are the most striking factor
16 for the low quality of care the women usually receive in low and middle-income
17 settings, contributing to the still high burden of maternal morbidity and mortality. If
18 we were successful in identifying such “specific patterns of physical activity and sleep”
19 as predictors for pregnancy complications, further validation studies will necessarily be
20 recommended for assessing its effectiveness for the whole management of such
21 conditions. Additionally, MAES-I will enable further specific studies among high risk
22 population and also will help to identify the best gestational age for monitoring, giving
23 the means to target a specific gestational age interval.
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Abbreviations

ANC – antenatal care	min – minutes
BMI – body mass index	mg – milligram
BP – blood pressure	mL – millilitre
CPM – count per minute	mmol – millimole
dL – decilitre	NICE – National Institute for Health and Care Excellence
FAQ – frequently asked questions	PA – physical activity
h – hour	PI – Principal investigator
HDI – human development index	SE – sleep efficiency
Hz - hertz	SCOPE – SCreening Of Pregnancy Endponits
Kg – kilogram	SOL – sleep onset latency
L – litre	TST – total nocturnal sleep time
MAES-I – maternal Actigraphy Exploratory Study I	US – United States
MEMS – microelectromechanical	USA – United States of America
MET – metabolic equivalents	w – week

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the overall study design and specific methodologies. RTS, JGC, JM, MLC and JPS conceived the study design. RTS, JGC, JM, and RBG planned the implementation of the study. RTS, JM, MLC and JGC drafted the manuscript. All authors discussed and made important contributions to the manuscript, read and approved the final version for submission.

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Table 1. Participating centers in the Maternal Actigraphy Exploratory Study I (MAES-I)

<ul style="list-style-type: none">• The Maternity of CAISM, University of Campinas, in Campinas, SP, Brazil;<ul style="list-style-type: none">○ Local Principal Investigator: Maria Laura Costa.
<ul style="list-style-type: none">• Maternity of the Clinic Hospital, Federal University of RS, Porto Alegre, RS, Brazil;<ul style="list-style-type: none">○ Local Principal Investigator: Janete Vettorazzi.
<ul style="list-style-type: none">• Maternity of the University Hospital, Jundiaí Medical School in Jundiaí, SP, Brazil;<ul style="list-style-type: none">○ Local Principal Investigator: Ricardo Porto Tedesco.
<ul style="list-style-type: none">• Maternity of Clinic Hospital, Federal University of Pernambuco, in Recife, PE, Brazil;<ul style="list-style-type: none">○ Local Principal Investigator: Edilberto A Rocha Filho.
<ul style="list-style-type: none">• MEAC – School Maternity of the Federal University of Ceará, in Fortaleza, CE, Brazil.<ul style="list-style-type: none">○ Local Principal Investigator: Francisco Edson de Lucena Feitosa.

Table 2. Inclusion and Exclusion Criteria of MAES – I**Inclusion Criteria**

- Singleton pregnancy
- Nulliparous (no previous delivery \geq 20weeks)
- Between 4+0 – 21+0 weeks of gestation

Exclusion Criteria

- | | |
|---|--|
| • Unsure LMP and unwilling to have to date the Ultrasound | • Major Uterine Anomaly |
| • \geq 3 Miscarriages | • Cervical Suture |
| • Major Fetal Anomaly/Abnormal Karyotype* | • Knife cone biopsy |
| • Essential Hypertension Treated Pre-pregnancy | • Ruptured membranes |
| • Mod-Severe Hypertension at booking (\geq 160/100 mmHg) or Chronic hypertension using antihypertensive medication | • Use of long-term steroids |
| • Pre-pregnancy Diabetes | • Use of Low-dose Aspirin |
| • Renal Disease | • Use of Calcium (> 1g/24h) |
| • Systemic Lupus Erythematosus | • Use of Eicosapentaenoic acid (fish oil) > 2,7g |
| • Anti-phospholipid Syndrome | • Use of Vit. C \geq 1000mg & Vit. E \geq 400 UI |
| • Sickle Cell Disease | • Use of Heparin/LMW Heparin |
| • HIV or Hep B or Hep C positive | • Untreated Thyroid disease |
| • Any condition that limits practice of physical activity | • Use of antidepressant and/or anxiolytic agents |

* All information regarding fetal anomalies will be properly recorded

Table 3. Measurement frequency and maximum return periods according to gestational age – MAES I

Gestational age	Measurement frequency	Maximum return period (weeks)
19 – 32 weeks	20Hz	4
33 – 36 weeks	30Hz	2
37 – 42 weeks	50Hz	1

Table 4. Performance of wrist and hip actigraphy methods according to different activities

	Hip			Wrist		
	Sens	Spec	BA	Sens	Spec	BA
Sitting	0.894	0.923	0.908	0.883	0.870	0.876
Vehicle	0.870	0.987	0.929	0.823	0.964	0.893
Walking/running	0.687	0.981	0.834	0.574	0.983	0.779
Standing	0.797	0.929	0.851	0.687	0.904	0.795
Average	0.812	0.955	0.881	0.742	0.930	0.836

BA: balanced accuracy; sens: sensitivity; spec: specificity

Adapted from Ellis K *et al.* Hip and Wrist Accelerometer Algorithms for Free-Living Behavior Classification. *Med. Sci. Sports Exerc.* 2016.

Table 5. Severe Neonatal Morbidity definition according to term/preterm status

Preterm	Term
Grade III and IV intraventricular haemorrhage	Grade II or III hypoxic ischemic encephalopathy
Chronic lung disease (home on O ₂ or on O ₂ at 36 weeks gestation)	Ventilation>24 hours
Necrotizing enterocolitis	Neonatal intensive care admission >4 days
Retinopathy of prematurity, stage 3 or 4	Apgar score <4 at 5 mins
Sepsis (blood or CSF culture proven)	Cord arterial pH<7.0 and/or base excess>-15
Cystic peri-ventricular leukomalacia	Neonatal seizures

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3 **Figure legends:**
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6 **Figure 1.** Set points of MAES-I study

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8 **Figure 2.** Estimated prevalence of preterm birth and preeclampsia according to
9 gestational age (RED represents majority of cases) and period of evaluation of PA and
10 sleep patterns (in GREEN)
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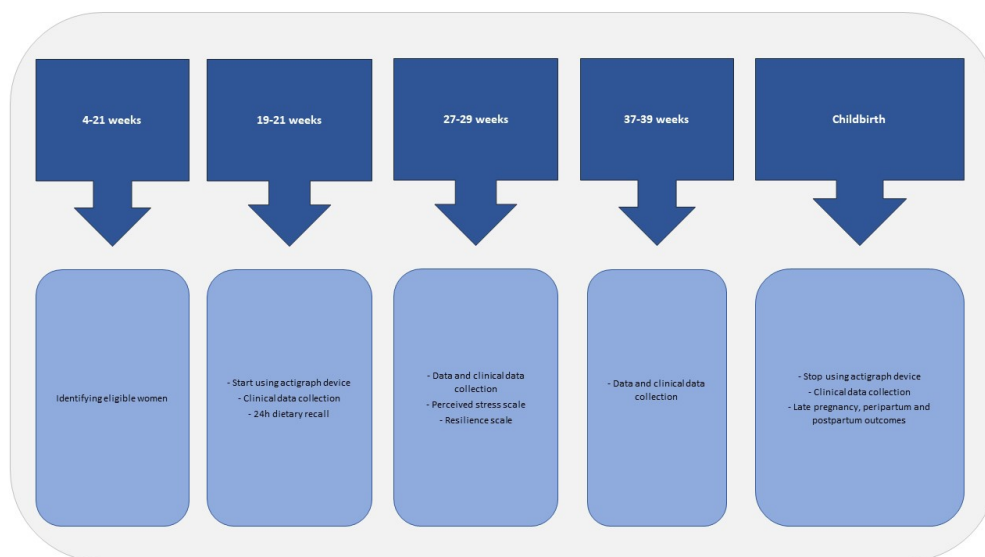


Figure 1

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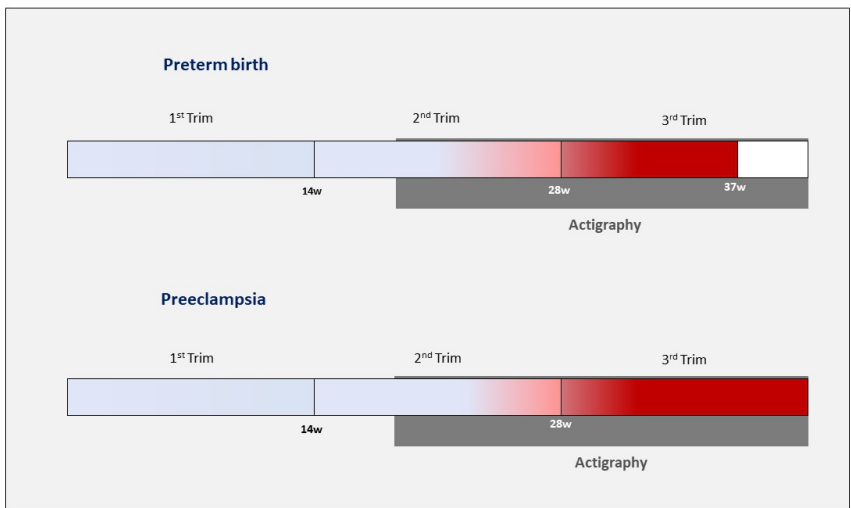


Figure 2

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BMJ Open

The identification of earlier predictors of pregnancy complications through wearable technologies in a Brazilian multicenter cohort: Maternal Actigraphy Exploratory Study I (MAES-I) study protocol

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Primary Subject Heading:	Obstetrics and gynaecology
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Keywords:	wearable technologies, actigraph, physical activity, sleep patterns, pregnancy complications

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STUDY PROTOCOL

The identification of earlier predictors of pregnancy complications through wearable technologies in a Brazilian multicenter cohort: Maternal Actigraphy Exploratory Study I (MAES-I) study protocol

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1 **Abstract**

2 **Introduction:** non-invasive tools capable of identifying predictors of maternal
3 complications would be a step forward in the improvement of maternal and perinatal
4 health. There is association between modification of physical activity (PA) and sleep-
5 wake patterns and the occurrence of inflammatory, metabolic, pathologic conditions
6 as chronic diseases. The actigraph device is validated to estimate PA and sleep-wake
7 patterns and might be valuable to identify predictors for maternal complications,
8 widening the window of opportunity to prevent, diagnose or treat specific conditions
9 prior to the development of typical symptoms or clinical signs, assessing PA and sleep-
10 wake patterns during pregnancy.

11 **Methods and analysis:** A cohort will be held in 5 centres from the Brazilian Network
12 for Studies on Reproductive and Perinatal Health. MAES-I will enroll 400 low-risk
13 nulliparous women that will wear the actigraph device on the wrist during day and
14 night (24h/day) uninterruptedly from 19-21 weeks until childbirth. Changes in PA and
15 sleep-wake patterns through pregnancy will be analyzed, considering gestational age
16 ranges, in women with and without maternal complications during pregnancy, such as
17 preeclampsia, preterm birth (spontaneous and provider-initiated), gestational
18 diabetes, maternal haemorrhage and also perinatal outcomes. A predictive model for
19 screening pregnant women for risk of specific adverse maternal and perinatal
20 outcomes is planned to be then developed using the actigraphy data.

21 **Ethics and Dissemination:** MAES-I study has been reviewed and approved by each
22 Institutional Review Board (IRB) and also by the National Council for Ethics in Research.
23 Detailed information of the study is provided in the Brazilian Cohort website
24 (www.medscinet.com/samba) and findings will be publicized in scientific literature and
25 Institutional webpages.

26 **Keywords:** wearable technologies; actigraph; physical activity; sleep patterns; sleep-
27 wake cycle; prediction; pregnancy complications.

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3 **1 Strengths and limitations of this study**
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- This multicentre cohort will collect comprehensive data on the main maternal and perinatal complications as pre-eclampsia, small for gestational age/fetal growth restriction, preterm birth and gestational diabetes mellitus.
 - Physical activity and sleep patterns will be estimated through an innovative wearable device used in the natural environment of the study subject.
 - Physical activity and sleep patterns will be estimated from the beginning of the second half of pregnancy until delivery, covering a wide interval during pregnancy and enabling the study of PA and sleep patterns changes throughout pregnancy.
 - One possible limitation refers to the uncovered first half of pregnancy regarding this information.

1 Background

2 Reducing the global maternal mortality ratio to less than 70 per 100,000 live births by
3 2030 is one of the targets of the new United Nations Sustainable Development Goals
4 [1]. Multiple challenges need to be tackled to achieve this target, but the 2016-2030
5 health and development agenda goes well beyond mortality reduction. The Global
6 Strategy for Women's, Children's and Adolescent's Health aims to ensure that every
7 newborn, women and child not only survive but thrive. This will only be possible if a
8 transformative agenda, with innovation at the central stage, is put into action [2].

9 One of the major challenges that need to be addressed is optimizing the recognition of
10 earlier predictors and identifiers of maternal and perinatal complications. Delays in
11 diagnosing and managing maternal complications have been associated with poor
12 outcomes [3]. The reduced self-perception of clinical signs related to maternal
13 complications, difficulties in accessing the health system and poor quality of care may
14 contribute to the late identification of complications and worsened prognosis. The
15 development of a non-invasive Antenatal Care (ANC) tool capable of identifying
16 maternal sub-clinical signs during pregnancy may provide the window of opportunity
17 for the earlier identification of abnormal patterns of physiologic parameters related to
18 pregnancy complications. We consider earlier identification when the recognition
19 could be made before clinical presentation, when standard criteria based on clinical
20 signs, symptoms, and supplementary tests are presented. Shortening the time
21 between the onset of a complication and the initiation of the appropriate
22 management allow for secondary prevention and reduction of maternal morbidity and
23 mortality [3–7].

24 Pervasive computing (i.e. the trend towards embedding microprocessors in everyday-
25 life objects so they can generate data) and wearable technology (i.e. clothing and
26 accessories incorporating computer and advanced electronic technologies such as
27 wrist and/or waistband sensors) are ubiquitous and able to generate a new dataset
28 that needs to be correlated with pregnancy outcomes. Preterm birth and
29 preeclampsia, for instance, are two important pregnancy complications that have a
30 relatively long subclinical phase before the appearance of signs or symptoms [8, 9]. It is
31 plausible that during this subclinical phase of certain conditions the pattern of physical

1 activity (PA) or sleep-wake rhythm is affected in some way and this change could be
2 captured through wearable devices. Although some studies show that PA patterns
3 (actigraphy parameters) may be related to systemic inflammation and diseases in the
4 general population [10, 11], published literature correlating wearable technology data
5 and maternal complications are very scarce.

6 The human circadian rhythm is ruled by endogenous physiologic mechanisms and
7 environmental stimuli [12]. There is solid evidence showing that modification of
8 circadian rhythm or sleep and PA patterns are an underlying condition related to
9 inflammatory, degenerative and/or metabolic chronic diseases as diabetes,
10 hypertension, and cancer [13]. Circadian misalignment is defined as having
11 inappropriate timed sleep and wake, misplaced feeding periods and modification of
12 activity behavior.

13 The determination of cause or consequence effect between these modifications and
14 the development of pathological conditions is a complex task. It seems that changes in
15 appetite-stimulating hormones, glucose metabolism, inflammatory markers, and mood
16 are some of the related pathways [13–15]. Leproult *et al.* evaluated the effect of
17 circadian misalignment on metabolic and inflammation markers in cardiovascular
18 disease [15]. The insulin action and release, and also the levels of some inflammatory
19 markers that are predictors for cardiovascular diseases, were abnormal in individuals
20 with circadian misalignment. The mechanisms involved in the association between
21 changes of PA pattern and pathologic conditions seem to be of multiple etiologies. Sani
22 *et al.* assessed the circadian rhythm of more than 2,300 African descendant adults. More
23 than evaluating physical activity itself, the authors aimed to identify chronobiologic
24 patterns of adults from different socioeconomic settings. The study identified that
25 chronobiologic behavior can vary depending on individual BMI, socioeconomic
26 background, work type and time of sunlight exposure. Possibly, many other factors are
27 involved in modifications of chronobiologic behavior, such as pathologic conditions.
28 Some metabolic, cognitive, cardiovascular and other chronic degenerative diseases
29 have been associated with particular patterns of PA and sleep [10, 11, 16–18]. A
30 previous observational study assessed various sleep parameters during pregnancy, e.g.
31 sleep onset latency (SOL), wake after sleep onset (WASO) and total nocturnal sleep

1 time (TST). Difficulty in initiating sleep in early pregnancy was associated with higher
2 body mass index, greater weight gain and higher blood pressure during pregnancy
3 [17]. Palagini *et al.* reviewed clinical evidence between chronic sleep loss and
4 pregnancy adverse outcomes, discussing common mechanisms of stress system
5 activation [19]. Low-quality evidence suggests an association between sleep loss and
6 prenatal depression, gestational diabetes, preeclampsia, abnormal length of labour,
7 caesarean delivery, abnormal fetal growth, and preterm birth. Those results
8 corroborate with other findings regarding pregnancy and sleep disorders [20–23].

9 The assessment of PA and the sleep patterns can be performed using small wrist (or
10 waist) devices similar to a regular watch (actigraphy technology). The type of sensor,
11 batteries, materials and output data have been substantially developed in recent
12 years, enabling low cost, comfort, discretion and performance [24]. Nowadays there
13 are devices that are portable, lightweight and with a large capacity to storage
14 information, including a software with automatic scoring algorithms packages for the
15 detection of wakefulness, sleep periods and PA [24, 25]. The actigraphy estimation of
16 PA and sleep patterns is validated as a proxy for chronobiologic behavior [26–29] and 7
17 to 14 days using the actigraph device provides reliable estimates of PA behavior in
18 older adults [30–32]. Both hip and wrist devices show reliable and acceptable
19 performance in estimating PA and sleep-wake patterns [33–36].

20 The main advantages of using wearable devices for actigraphy is the non-invasiveness,
21 24/7 monitoring of the circadian pattern and PA, and informing sleep habits and
22 parameters in the user natural environment [24, 25, 28]. We propose an innovative
23 and strategic approach to monitor PA and sleep-wake patterns during pregnancy,
24 establishing a large database comprised of clinical, epidemiological, PA and sleep-wake
25 variables potentially capable of composing a prediction model for maternal
26 complications during pregnancy. The main goal of this study is to identify earlier
27 predictors of pregnancy complications by correlating data generated on PA and sleep
28 patterns through wearable devices (wristband sensors) with maternal and perinatal
29 complications and outcomes.

30 **Methods/Design**

1 **Study design**

2 We will conduct a cohort study of 400 low-risk pregnant women using wrist sensor
3 bands able to capture information on daily physical activity and sleep patterns
4 (exposure). This cohort study will be implemented in 5 ANC clinics linked to obstetric
5 units in 3 different regions of Brazil that are already part of the Brazilian Network for
6 Studies on Reproductive and Perinatal Health [37], as shown in Table 1. During a
7 period of eight months, the ANC clinics will identify eligible cases for using the
8 wristband sensors. Wearable technology data will be correlated with the occurrence
9 of pregnancy and childbirth complications and outcomes, thus understood as an
10 effect.

11 Eligible women will be identified up to 21 weeks of gestation and invited to participate.
12 A proper consent form will be applied and the women who agree to participate will
13 receive a wristband sensor to be used starting at 19-21 weeks until childbirth,
14 uninterruptedly.

15 **Study setting and population**

16 Brazil is a multi-ethnic mixed-race population of diverse resourced settings [38].
17 Despite the considered high global overall human development index (HDI 0.727) in
18 2010, the HDI of Brazilian municipalities ranged from 0,862 to 0,418 [39]. The
19 possibility of considering such mixed population is suitable to explore information
20 regarding maternal patterns of mobility and sleep, maximizing external validity and
21 comparisons to other populations. A few reasons might support the study population
22 focused in low-risk nulliparous women: 1) Previous obstetric history can refer to
23 known risk factors for many maternal complications such as preterm birth,
24 preeclampsia, and diabetes [13, 40]. Nulliparous women enable unbiased sampling
25 regarding obstetric history. 2) Women with previous morbidity such as hypertension,
26 diabetes, nephropathy or others chronic/degenerative diseases are more likely to
27 present abnormalities of sleep-wake rhythm or physical activity patterns during
28 pregnancy.

29 **Sampling**

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3 1 The five participating centers are regional referral obstetric units responsible for
4 2 antenatal care assistance mainly for high-risk pregnant women. Participating centers
5 3 are listed in Table 1. Nevertheless, there are primary health care units strategically
6 4 linked with these participating centers, enabling the identification and enrollment of
7 5 low-risk pregnant women. The recruitment strategies include approaching all eligible
8 6 women in these participating centers and their linked facilities. An informed consent
9 7 form will be applied for women who agree to participate.

8 *Eligible women: Low-risk pregnant subjects*

9 There is no international consensus on the criteria for low-risk pregnancies, although
10 there are several known factors associated with maternal and perinatal adverse
11 outcomes. A recent study evaluating complications of “low-risk” pregnancies of US
12 Americans (10 million births from 2011 through 2013) showed that 29% of low-risk
13 women had an unexpected complication requiring no routine obstetric/neonatal care
14 [41]. This shows the difficulty in establishing a “low-risk profile” for maternal/perinatal
15 complications. As an exploratory study, we tried to exclude potential known
16 confounders of pre-pregnancy conditions related to adverse maternal or perinatal
17 outcomes as shown in Table 2, in order to assess PA and sleep patterns of a mostly
18 “normal” population. Nonetheless, lifestyle habits and body composition (Body mass
19 index, height, etc.) characteristics, and some non-severe chronic diseases as non-
20 severe anaemia and/or asthma are not among exclusion criteria but may be part of
21 subgroup analyses (composition of any previous disorder, e.g.). Intra and inter-
22 individual analyses of PA and sleep patterns enable the identification of potential
23 confounders affecting primary outcomes, avoiding potential biases. It means that
24 comparison of PA and sleep pattern parameters collected in different stages of
25 pregnancy from the same participant (intra-individual analysis) and collected at the
26 same stage of pregnancy from different participants (inter-individual analysis) will be
27 carried out.

28 Eligible women will be enrolled between 04-21 weeks. The inclusion and exclusion
29 criteria are presented in Table 2.

30 ***Data collection methods***

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3 1 Essentially, MAES I study is comprised of 4 key set points – 3 clinical visits during
4 pregnancy and a postnatal visit. The clinical visits will be held at 1) between 19-21
5 2 weeks; 2) between 27-29 weeks; 3) between 37-39 weeks. At first, second, third and
6 3 postnatal visits, additional information regarding maternal history, details on
7 4 pregnancy complications, maternal biophysical data (weight, height, skinfolds) and
8 5 pregnancy adverse outcomes will be collected following a specific Standard Operating
9 6 Procedure (SOP) specially developed for MAES-I study. Additionally, the Perceived
10 7 Stress Scale [42] and Resilience Scale [43] will be applied during 27-29w visit. Figure 1
11 8 shows the set points of MAES-I study.
12 9

13 10 Eligible women will be invited to use a small wrist device similar to a regular watch
14 11 (GENEActiv Original – Activinsights®). The device contains sensors that estimate PA and
15 12 sleep-awake patterns through a proper software algorithm. At the first set point of
16 13 MAES-I study (between 19+0 - 21+0 weeks of gestation), eligible women who agreed
17 14 to participate will start using the wrist bracelet device on the non-dominant arm
18 15 during day and night (24h/day) uninterruptedly until childbirth (including bathing or
19 16 aquatic activities). The acquisition of actigraphy data can be performed in different
20 17 frequencies (from 10Hz to 100Hz). Since the frequency of data acquisition impacts on
21 18 the battery life of the device (inverse relationship), the measurement frequency will be
22 19 set up according to the participant's gestational age (Table 3). This information will be
23 20 registered in the database accordingly. The data accumulated will be downloaded
24 21 during participant's antenatal care visits, according to the maximum return periods
25 22 showed in Table 3. The maximum return periods were calculated taking into
26 23 consideration the expected battery life. At each antenatal care visit, the used device
27 24 will be returned to the research team and a new charged device will be provided to the
28 25 participant.

29 26 A leaflet with detailed information and FAQ (Frequently asked questions) on the device
30 27 will also be provided to the women. They will also have a cell phone number to call
31 28 whether doubts arise regarding the procedures for using the device, or if any technical
32 29 or medical concern arises.

33 30 All actigraphy data collected will be entered into proper software to interpret data and
34 31 generate an output file. Then, the actigraphy data will be uploaded to an online

1 database platform developed by MedSciNet®, where all clinical data of the study will
2 also be registered. The actigraphy software uses several algorithms to estimate
3 physical activity and sleep patterns. The database is centralized, secure, internet-
4 based and allows several procedures for prospective and retrospective monitoring,
5 hierarchical access (local user, general manager, etc.). The database will be translated
6 into Portuguese and English, facilitating data collection for Portuguese-speaking team
7 and international monitoring. A correspondent paper form will be available for data
8 collection if necessary (e.g. internet connection failure for instance).

9 *Decision to start monitoring PA and sleep patterns between 19-21 weeks*

10 There are various underlying mechanisms involved in the development of the maternal
11 and perinatal adverse outcomes that will be assessed, as preterm birth, preeclampsia,
12 gestational diabetes, fetal growth restriction and small for gestational age. The pre-
13 clinical phase, stage where there are no clinical signs or symptoms, might be different
14 for each disease and dependent on environmental and individual aspects. The study of
15 adverse maternal and perinatal predictors has been focused in early pregnancy so far
16 (first trimester, <14 weeks of gestation), aiming to maximize the window of
17 opportunity for preventative interventions. However, we hypothesized that the
18 modification of PA and/or sleep pattern due to maternal underlying changes of
19 biological function might not be evident at a very early stage in pregnancy before the
20 beginning of the pre-clinical phase. Our hypothesis is that it possibly occurs shortly
21 before symptoms.

22 Additionally, we took into account that the occurrence of the main maternal
23 complications, as preeclampsia, fetal growth restriction, and preterm birth, are more
24 common in late pregnancy to establish the period between 19-21 weeks as
25 appropriate to start the assessment of PA and sleep patterns. A recent cross-sectional
26 study conducted in 20 referral centres in Brazil, including the five participating centres
27 of this proposal, showed that the occurrence of preterm birth before 28 weeks
28 comprised less than 1% of all births and less than 8% of all preterm births [44]. In
29 addition, the early onset of preeclampsia (before 34 weeks of gestation) complicates
30 less than 0.4% of all pregnancies, according to a large retrospective cohort of more
31 than 450,000 deliveries in USA [45]. Figure 2 outlines the predicted prevalence of

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3 1 preterm birth and preeclampsia in the second trimester, highlighting its clinical
4 2 presentation, when classic symptoms and signs of a certain disease/complication are
5 3 presented, through pregnancy in red. Our hypothesis is that PA and sleep patterns
6 4 might be altered closely to the clinical presentation, still in preclinical phase when
7 5 there is no symptoms or signs.

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12 6 In brief, as an exploratory study, we indeed needed to make an arbitrary decision
13 7 regarding interval of monitoring PA and sleep patterns. For that, we had taken into
14 8 consideration: 1) the main maternal/perinatal complications of interest occur in the
15 9 second half of pregnancy, more precisely in late pregnancy (Figure 2); 2) we
16 10 hypothesize that any potential change on PA or sleep patterns might occur days or
17 11 weeks before the onset of maternal or perinatal complication. Then, we focused
18 12 monitoring women during second half of pregnancy.

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24 13 Thus, the start of assessment between 19-21 weeks seems to be very reasonable,
25 14 providing a wide interval to monitor and predict the main maternal and perinatal
26 15 adverse outcomes.

27 28 29 30 16 *Actigraph device*

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34 17 The actigraph device that will be used to monitor PA and sleep-wake patterns is
35 18 GENEActiv Original (GENEActiv, Activinsights Ltd, Huntingdon, UK). The device has
36 19 multiple sensors as microelectromechanical (MEMS) accelerometer, temperature
37 20 (linear active thermistor) and light (silicon photodiode), providing crude raw data for a
38 21 variety of applications.

39 40 41 22 *Wrist vs waist wear: advantages and performance*

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43 23 Wrist wear of actigraph devices provides more comfortable use during wake and sleep
44 24 periods and highest wear time compared to waist monitors [33, 46]. A non-systematic
45 25 review published in 2011 showed that actigraphy is a useful and reliable tool to assess
46 26 sleep patterns and circadian rhythm disorders, although there are some limitations on
47 27 diagnosing sleep diseases or measuring sleep stages [25]. Actigraphy showed excellent
48 28 concordance with polysomnography in assessing sleep parameters in healthy subjects
49 29 (sensitivity >90% in estimating total sleep time, for instance). A recent study evaluated
50 30 the concordance of physical activity estimation of wrist device in free-living settings in

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3 1 forty overweight or obese women [34]. They used both wrist and hip devices, and a
4 2 small camera that captured participant behaviour for 7 days, enabling the monitoring
5 3 of physical activity behaviour (gold-standard comparison). The hip and wrist machine
6 4 learning (ML) classifiers used are different due to the different methods/algorithms to
7 5 estimate physical activity [34]. The sensitivity and specificity of hip and wrist
8 6 estimations according to Ellis *et al* are showed in Table 4 [34].

9 7 Two years ago, the same author had published a similar evaluation using 40 adults
10 8 (women and men), showing that the hip and wrist accelerometers obtained an average
11 9 accuracy of 92.3% and 87.5%, respectively, in predicting PA types [47].

12 10 Staudenmayer *et al* developed an investigation with 20 participants also using two
13 11 devices (wrist- and hip- worn), and showed that wrist actigraphy can estimate energy
14 12 expenditure accurately and relatively precisely [48]. Another study evaluating PA
15 13 patterns in a free-living environment with wrist devices showed that women in the top
16 14 40% or bottom 40% of the distribution of daily PA, hip and wrist accelerometers
17 15 agreed on the classification for about 75% of the women [49]. Additionally, the total
18 16 activity (counts per day) was moderately correlated (Spearman's $r = 0.73$) between the
19 17 wrist and hip worn devices.

20 18 At the best of our knowledge, there are no systematic reviews or other high-quality
21 19 evidence-based recommendation supporting a particular method. Although wrist wear
22 20 of actigraphy is not the more traditional method, it might be the best choice for
23 21 assessing long periods of PA or sleep patterns, even more considering the similar
24 22 performance of the waist wear. The current proposal does not intend to diagnose
25 23 pathologic behaviours or diseases, but to identify different patterns along pregnancy
26 24 and in different subgroups of women. Therefore, supported by the evidence that wrist
27 25 wear of actigraphy devices can accurately and more comfortably estimate PA and
28 26 sleep patterns, mainly for long periods and in the free-living environment, the MAES-I
29 27 study group adopted wrist wear devices.

30 28 **Main variables**

31 29 The independent variables assessed as potential predictors of maternal complications
32 30 will be related to sleep-wake cycle and mobility as:

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3 1 *“Sleep” variables*

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5 2 - Sleep onset latency (SOL): time elapsed between full wakefulness to sleep.
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7 3 - Total sleep time (TST): The amount of actual sleep time in a sleep episode
8 (excludes awakes).
9
10 4
11 5 - Wake after sleep onset (WASO): defined as total amount of time awake after sleep.
12 6 - Sleep Efficiency (SE): the proportion of sleep in the period potentially filled by
13 7 sleep-ratio of total sleep time to time in bed.

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16 8 The actigraph collects many pieces of information related to body position and
17 9 body movements to estimate the described sleep variables. Then, actigraphy software
18 will be used to analyse the data and generates the output variables.
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21 11 *“Physical activity” variables*

22
23 12 Actigraphy technology estimates physical activity through various parameters
24 13 collected by the actigraph device. Briefly, according to Freedson *et al*, the triaxial
25 14 sensors stressed by acceleration forces can estimate the intensity of movements. The
26 15 acceleration signal is converted to digital signal and summed over a user specified
27 16 time interval (epoch). At the end of each epoch the activity count is stored. Then,
28 17 according to Count per minute (CPM) cut points, the PA intensity can be categorized
29 18 [50]. The information is translated by the software using proper algorithms into
30 19 quantitative variables as following:

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38 20 - Sedentary time (hours/day): the number of hours per day of count per minute
39 21 between 0-99.
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42 22 - Light activity (hours/day): the number of hours per day having count per minute
43 23 between 100 - 1951.
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46 24 - Moderate activity (minutes/day): the number of hours per day having count per
47 25 minute between 1952 - 5724.
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50 26 - Vigorous activity (minutes/day): the number of hours per day having count per
51 27 minute between 5725 - 9498.
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54 28 - Very vigorous activity (minutes/day): the number of hours per day having count
55 29 per minute between 9499 - ∞.

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3 1 - MET rates: Metabolic Equivalents (METs) are commonly used to also express
4 2 the intensity of physical activities. One MET is the energy cost of resting quietly,
5 3 often defined in terms of oxygen uptake as $3.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. MET rate
6 4 expresses a person's working metabolic rate relative to their resting metabolic
7 5 rate. Briefly, the triaxial piezoelectric sensors stressed by acceleration forces can
8 6 estimate the intensity of movements, converted to the oxygen consumption
9 7 required to perform such movement.
10 8
11 8 - Step counts/day: estimated steps count per day (estimated by proper
12 9 algorithms using accelerometer data.)
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19 *Outcomes*

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21 The primary outcomes are late pregnancy complications as:

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23 12 - Preeclampsia: Hypertension after 20 weeks of gestation, systolic BP $\geq 140\text{mmHg}$
24 13 and/or diastolic BP $\geq 90\text{mmHg}$ (Korotkoff V) on at least 2 occasions 4h apart with:
25 14 1) Proteinuria $300 \text{ mg}/24\text{h}$ or spot urine protein: creatinine ratio $30 \text{ mg}/\text{mmol}$
26 15 creatinine or urine dipstick protein $\geq (+)$ OR, in the absence of proteinuria,
27 16 hypertension and 2) any multi-system complication that are: Haematological
28 17 abnormalities; thrombocytopenia (platelets $< 100 \times 10^9/\text{L}$); Disseminated
29 18 intravascular coagulation (DIC), and haemolysis; Liver disease: increased
30 19 aspartate transaminase and/or alanine transaminase $> 45 \text{ IU}/\text{L}$ and/or severe
31 20 right upper quadrant or epigastric pain, liver rupture; Neurological problems:
32 21 eclampsia, imminent eclampsia (severe headache with hyperreflexia and
33 22 persistent visual disturbance), cerebral haemorrhage; Acute renal insufficiency:
34 23 new increase in serum creatinine to $> 100 \text{ mmol}/\text{L}$ antepartum or $> 130 \text{ mmol}/\text{L}$
35 24 postpartum; Pulmonary oedema confirmed by chest x-ray [51].
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39 25 - Gestational Diabetes: new diabetes developing in pregnancy according to the WHO
40 26 recommendation [52] that defines gestational diabetes as having:
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- Fasting plasma glucose $\geq 92 \text{ mg}/\text{dl}$, or
 - 1-h plasma glucose tolerance test (75g load) $\geq 180 \text{ mg}/\text{dl}$, or
 - 2-h plasma glucose tolerance test (75g load) $\geq 153 \text{ mg}/\text{dl}$.

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3 1 - Spontaneous Preterm Birth: spontaneous onset of preterm labour or premature
4 rupture of membranes leading to preterm birth, childbirth before 37 weeks of
5 gestation.
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8 4 - Provider-Initiated Preterm Birth: defined as childbirth occurring at less than 37
9 weeks, medically indicated due to maternal/fetal compromise or both;
10
11 6 - Maternal Hemorrhage: Classified in 1) Antepartum haemorrhage defined as
12 bleeding from the genital tract after 24 weeks of gestation; 2) Primary Postpartum
13 haemorrhage as the loss of 500 ml blood or more from the genital tract within 24
14 hours of the childbirth.
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19 Secondary outcomes include childbirth variables and neonatal adverse outcomes as
20 fetal death, caesarean section, small for gestational age (defined as birth weight below
21 percentile 10 for gestational age), Apgar score < 7 at 5 minutes, neonatal severe
22 morbidity (Table 5) and neonatal mortality before discharge.
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26 ***Plans for analyses***

27 *Sample size estimation*

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30 This is an exploratory and innovative study focused on a specific population (pregnant
31 women) and therefore there are no previously published parameters available for
32 sample size estimation. Considering a relatively wide range of frequency of
33 complications arising in pregnancy from 3 to 20% (including preeclampsia, fetal growth
34 restriction, gestational diabetes, hemorrhage, preterm birth, etc.), a theoretical large
35 population size (above 1 million pregnant women), an acceptable margin of error of
36 4%, the involvement of 5 clusters (participating centers) and a 95% level of confidence,
37 384 women would be necessary. Therefore, we are rounding up this estimation for at
38 least 400 initially low-risk pregnant women to be enrolled in the study. We estimated
39 the incidence of some main maternal complications considering the following studies:
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- 48 - Pre-eclampsia: An international prospective cohort study with nulliparous women
49 called SCOPE used similar criteria for the low-risk profile, having 5% of incidence of
50 pre-eclampsia [53].
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3 1 - Preterm Birth: A recent cross-sectional study conducted in 20 referral obstetric
4 2 centres in Brazil, including the five participant centres of this proposal, showed a
5 3 prevalence of 12.3% of all births [44].
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8 4 - Gestational Diabetes: SCOPE international cohort, previously mentioned, had a
9 5 prevalence of 8.9% of gestational diabetes in low-risk screened nulliparous women,
10 6 according to mainly to the NICE guidelines [54].
11
12 7 - Fetal growth restriction/small for gestational age: SCOPE international cohort,
13 8 previously mentioned, had a prevalence of 10.7% of newborns small for gestational
14 9 age, according to the customized centiles of birthweight (<10%)[55].
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19 *Analyzes and statistics details*

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21 According to these studies above, the predicted incidence of these complications
22 seems reasonable and reproducible in our cohort. Then, sample size estimation might
23 assure enough cases of maternal and perinatal complications for the current proposal.
24

25
26 Firstly, we will identify PA and sleep-wake patterns of women who did not develop
27 adverse maternal or perinatal outcomes. It will permit the recognition of a normal PA
28 and sleep-wake patterns in low-risk population without complication during
29 pregnancy. Using the same population, we will analyze changes in PA and sleep-wake
30 patterns through pregnancy, allowing for gestational age periods.
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35 Then, we will compare the PA and sleep-wake patterns of women who developed
36 specific adverse maternal or perinatal outcomes with those who did not. The
37 differences between groups might be identified to be used as potential markers for
38 specific pregnancy complications.
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43 After that, we will analyze changes in PA and sleep-wake patterns of women who
44 developed adverse maternal or perinatal outcomes through pregnancy, comparing the
45 patterns and trying to discover which changes and when before the onset it would be
46 related to pregnancy complications. If possible, we will conduct subgroup analysis
47 including subpopulation with potential higher risk for maternal complications
48 (confounder variabls), including obesity, smoking, etc.
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3 1 Finally, we will develop a predictive model for screening pregnant women for risk of
4 2 specific adverse maternal and perinatal outcomes using PA and sleep-wake data
5 3 estimated with actigraphy technology.

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8 4 The analysis will be performed using the actigraph software that translates the
9 5 collected information into PA and sleep-wake parameters. Additionally, Friedman and
10 6 Wilcoxon for paired samples, t-test, and ANOVA for repeated measures will be applied
11 7 to achieve statistical analyses. Also, we will address sensitivity, specificity and
12 8 likelihood ratio for altered PA and sleep patterns or for their changes throughout
13 9 pregnancy.

10 ***Discontinuation of participants***

11 The criteria for discontinuation include:

- 12 - Withdrawal of consent;
- 13 - Not regularly using the actigraph device for long periods, less than 50% of all
14 planned time. The information that they are not using the device properly will be
15 recorded if women notice the MAES-I team. Otherwise, the low use of the device
16 will be noticed after data discharge during antenatal care visits.
- 17 - The loss to follow-up, not allowing the download of actigraphy data.

18 ***Data and Sample Quality***

19 All entered data will be prospectively and retrospectively monitored by local research
20 assistants and a global monitor. Internal consistency of variables will be constantly
21 performed by the database and error messages are automatically flagged. A local
22 research assistant will be responsible for checking all forms and actigraphy data before
23 locking forms, assuring good quality of data (double-checking entered data and
24 checking for inconsistencies between variables, for instance). Then, the local principal
25 investigator (PI) will be responsible for signing the case, enabling its incorporation to
26 the final database. The University of Campinas will coordinate, implement and monitor
27 the study in the five participating centres. A general manager and a global monitor are
28 also part of the team of the coordinating centre. The local team of each participating
29 centre is comprised of a Local PI and research assistants.

30 ***Ethics and Dissemination***

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3 1 MAES-I study focuses on low-risk nulliparous Brazilian pregnant women. Despite being
4 2 considered of low risk for maternal and perinatal complications, they are not free of
5 3 suffering complications. Furthermore, the first and second delays, defined as a delay in
6 4 deciding to seek care and delay in reaching a health care facility [56], are not
7 5 uncommon, establishing a barrier between earlier recognition of symptoms and timely
8 6 interventions capable to successfully treat potentially life-threatening conditions. We
9 7 believe that women will feel encouraged, empowered and willing to participate in the
10 8 study that aims to develop a potentially useful prenatal care tool to identify the risk for
11 9 maternal and perinatal morbidity and mortality. Following national ethical regulations,
12 10 the participants will not receive any financial compensation.

11 11 Women who agree to participate in the study will not have any disadvantages or injury
12 12 of their prenatal care. On the contrary, they will receive a telephone number to
13 13 contact the clinical researchers at any time (24/7 service), which enables a closer
14 14 contact with researchers and providers of care, since the MAES-I team are committed
15 15 to contacting providers of care if any potential complication is noticed by participants.

16 16 The participating women will not be responsible if loss, theft or damage to the wrist
17 17 device occurs. However, they will be asked to return the device after they finished the
18 18 participation in the study, in order to use it for new women entering the study. No self-
19 19 damage is expected in those who use the device.

20 20 Participating women will not be able to identify any PA or sleep parameters at any
21 21 stage of the study. The download of the data is only possible through the own licensed
22 22 software of the device. Actigraphy devices provided for participating women have a
23 23 unique code which will be recorded in the database together with the interval of use
24 24 for each women. Actigraphy data will be labelled using participant ID, device number,
25 25 gestational age when starting using each device and return date of each device. The
26 26 use of such codes, ID`s and numbers will ensure confidential identify for all
27 27 participating women. The identity of all women will be kept confidential.

28 28 MAES-I study has been reviewed and approved by the National Committee for Ethics in
29 29 Research of Brazil (CONEP) and by the Institutional Review Board (IRB) of the
30 30 coordinating centre (Letter of approval 1.834.116 issued on 24th November 2016) and

1 of all other Brazilian participating centres. All women who will be enrolled in the
2 MAES-I cohort will sign an informed consent form.

3 The ethical principles stated in the Brazilian National Health Council (Resolution CNS
4 466/12) will be respected in every stage of this study. The anonymity of the source of
5 information will be guaranteed and the care for the women will be provided
6 independently of her agreement to participate in the study. The study also complies
7 with the Declaration of Helsinki amended in Hong Kong in 1989. The methodological
8 and ethical aspects of MAES-I study protocol were developed following STROBE
9 guidelines [57].

10 *Patient and Public Involvement*

11 Patients and public were not involved in this study for the development of the
12 research question and outcome measures. However, the choice for a wrist device was
13 based on the preference of users as reported. Participants of the study will have access
14 to the results by its webpage that will be open access.

15 Detailed information of the study is provided in the Brazilian Cohort website
16 (www.medscinet.com/samba) and findings will be publicized in scientific literature and
17 Institutional webpages. We intend to disseminate our findings in scientific peer-
18 reviewed journal, general free access website, specialists' conferences, and to our
19 funding agencies.

20 21 **Discussion**

22 The actigraphy is an innovative, non-invasive, non-operator dependent, wearable
23 technology, which enables the estimative under real life conditions of diverse variables
24 related to mobility, physical activity, sleep-wake, and circadian cycle patterns.
25 Actigraph devices show high sensitivity in sleep-wake parameters detection and are
26 currently highly recommended by the American Sleep Disorder Association for
27 diagnosis and therapy response of circadian rhythm disorders [27, 28, 58]. Although
28 some studies show that 7 to 14 days using the actigraph device provides reliable
29 estimates of physical activity behavior in older adult, it is not absolutely clear how
30 many days is needed to estimate habitual PA by using the wrist/waist device during

1 pregnancy. In general, it seems to depend mainly on the type of actigraph device,
2 position of wear and target population [30, 33]. Nevertheless, MAES-I study will
3 provide sufficient data to assess different patterns along pregnancy.

4 The use of wearable physical activity monitors has grown enormously due to the
5 interest about the relationship between the pathophysiology of diseases and physical
6 activity and sleep patterns. A recent study on the use of physical activity monitors in
7 human physiology research unravels the current and potential uses of actigraph device
8 as in strategies to promote healthier behaviour or to predict outcomes [59]. The
9 authors conclude that physical activity monitors, as others new 21st century
10 technologies, have already transformed physiology research, revolutionizing the way
11 we assess patients and opening new areas of interest. In addition, the use of objectives
12 measures to evaluate habitual sleep duration and outcomes in pregnancy is critical,
13 taking into account recent investigations reporting little agreement between objective
14 and subjective assessments of sleep time [60].

15 Alterations in sleep patterns, as less deep sleep and more nocturnal awakenings, can
16 be observed in pregnancy as early as 10-12 weeks gestation [61]. Sleep disturbances
17 during pregnancy have been associated with preterm delivery, gestational
18 hypertensive disorders, glucose intolerance and increased risk of caesarean delivery
19 [19]. Shorter night time sleep was also associated with hyperglycemia [62]. Persistent
20 sleep deficiency is correlated with depressive symptoms and stress perception by
21 pregnant women [61]. These studies lay correlation between PA patterns and sleep
22 disturbances determining complications, in a well-established relationship of cause and
23 consequence, although sometimes it could not be adequately determined due to the
24 study design [17].

25 In a distinct way, our analysis intends to figure out if the maternal complication could
26 be identified by physical activity and/or sleep patterns modifications, even during its
27 pre-clinical period, previous the appearance of clinical signs. Considering the existing
28 evidence, we speculate that the PA and/or sleep patterns change days or weeks before
29 the clinical presentation of the complication. In general, the signs and symptoms of
30 some maternal outcomes are part of the gold-standard criteria for diagnosis (high
31 blood pressure, proteinuria and/or edema in the case of preeclampsia; premature

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3 1 contractions and cervical ripening/dilation in preterm birth; abnormal placental blood
4 2 flow and insufficient fetal growth in Intrauterine Growth Restriction). We acknowledge
5 3 the fact that there are potential confounders and limitations in predicting maternal and
6 4 perinatal complications using PA and sleep patterns estimated by actigraph devices.
7
8 5 We expect that our studied population will have different subgroups of women with
9 6 different risks and associated factors playing a role on maternal complication. It
10 7 includes obesity, smoking, extremes of age, for instance. None of those factors was
11 8 considered exclusion criteria and, if possible, we intend to assess subgroup analysis for
12 9 those maternal subgroups at they might present different PA and sleep patterns.
13 10 Nonetheless, we decided to perform a pragmatic approach, not excluding such
14 11 common factor from our sample.

15
16 12 The use of actigraph device during prenatal visits has a potential to become a new tool
17 13 to monitor pregnant women, improving maternal health care, identifying altered PA
18 14 and/or sleep patterns, measured objectively through actigraphy, before the occurrence
19 15 of those signs and symptoms. Therefore, the focus would be offering new technology
20 16 to monitor the development of a potential maternal complication. Other positive
21 17 points of our study are the period of data collection (from 19 weeks till delivery) and
22 18 the low-risk profile of the cohort. Through which, it would be possible to describe a PA
23 19 and sleep patterns in a low-risk pregnant population and better interpret actigraphy
24 20 data among pregnant women. The current clinical and biological predictors for the
25 21 main maternal complications as preeclampsia, preterm birth, maternal haemorrhage,
26 22 and gestational diabetes still lack for effective sensitivity and specificity.

27
28 23 If this is confirmed to be true, an important step will be achieved for a possible
29 24 introduction of screening non-invasive procedures during prenatal care with the
30 25 purpose of identifying women at higher risk of developing those conditions. Therefore,
31 26 they could receive specific orientation on prevention and earlier detection of the onset
32 27 of condition for taking immediate action to look for professional health care and
33 28 receiving appropriate interventions, avoiding delays that are the most striking factor
34 29 for the low quality of care the women usually receive in low and middle-income
35 30 settings, contributing to the still high burden of maternal morbidity and mortality. If
36 31 we were successful in identifying such “specific patterns of physical activity and sleep”

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1 as predictors for pregnancy complications, further validation studies will necessarily be
2 recommended for assessing its effectiveness for the whole management of such
3 conditions. Additionally, MAES-I will enable further specific studies among high risk
4 population and also will help to identify the best gestational age for monitoring, giving
5 the means to target a specific gestational age interval.

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1 Abbreviations

ANC – antenatal care	min – minutes
BMI – body mass index	mg – milligram
BP – blood pressure	mL – millilitre
CPM – count per minute	mmol – millimole
dL – decilitre	NICE – National Institute for Health and Care Excellence
FAQ – frequently asked questions	PA – physical activity
h – hour	PI – Principal investigator
HDI – human development index	SE – sleep efficiency
Hz - hertz	SCOPE – SCreening Of Pregnancy Endpoints
Kg – kilogram	SOL – sleep onset latency
L – litre	TST – total nocturnal sleep time
MAES-I – maternal Actigraphy Exploratory Study I	US – United States
MEMS – microelectromechanical	USA – United States of America
MET – metabolic equivalent	w – week
METs – metabolic equivalents	

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the overall study design and specific methodologies. RTS, JGC, JM, MLC and JPS conceived the study design and wrote the first version of the study protocol. In a first meeting, the protocol was discussed and incorporated suggestions from RBG, FEF, ERF, DFL, JV, RPT and DSS. RTS, JGC, JM, and RBG planned the implementation of the study and developed the necessary material. RTS, JM, MLC and JGC drafted the manuscript that was afterwards revised by all other authors who gave suggestions. All authors discussed and made important contributions to the manuscript, read and approved the final version for submission.

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Table 1. Participating centers in the Maternal Actigraphy Exploratory Study I (MAES-I)

<ul style="list-style-type: none">• The Maternity of CAISM, University of Campinas, in Campinas, SP, Brazil;<ul style="list-style-type: none">○ Local Principal Investigator: Maria Laura Costa.
<ul style="list-style-type: none">• Maternity of the Clinic Hospital, Federal University of RS, Porto Alegre, RS, Brazil;<ul style="list-style-type: none">○ Local Principal Investigator: Janete Vettorazzi.
<ul style="list-style-type: none">• Maternity of the University Hospital, Jundiaí Medical School in Jundiaí, SP, Brazil;<ul style="list-style-type: none">○ Local Principal Investigator: Ricardo Porto Tedesco.
<ul style="list-style-type: none">• Maternity of Clinic Hospital, Federal University of Pernambuco, in Recife, PE, Brazil;<ul style="list-style-type: none">○ Local Principal Investigator: Edilberto A Rocha Filho.
<ul style="list-style-type: none">• MEAC – School Maternity of the Federal University of Ceará, in Fortaleza, CE, Brazil.<ul style="list-style-type: none">○ Local Principal Investigator: Francisco Edson de Lucena Feitosa.

Table 2. Inclusion and Exclusion Criteria of MAES – I

Inclusion Criteria	
<ul style="list-style-type: none"> • Singleton pregnancy • Nulliparous (who had never given birth before) • Between 19+0 – 21+0 weeks of gestation 	
Exclusion Criteria	
<ul style="list-style-type: none"> • Unsure LMP and unwilling to have to date the Ultrasound • ≥ 3 Miscarriages • Major Fetal Anomaly/Abnormal Karyotype* • Essential Hypertension Treated Pre-pregnancy • Mod-Severe Hypertension at booking ($\geq 160/100$ mmHg) or Chronic hypertension using antihypertensive medication • Pre-pregnancy Diabetes • Renal Disease • Systemic Lupus Erythematosus • Anti-phospholipid Syndrome • Sickle Cell Disease • HIV or Hep B or Hep C positive • Any condition that limits practice of physical activity 	<ul style="list-style-type: none"> • Major Uterine Anomaly • Cervical Suture • Knife cone biopsy • Ruptured membranes • Use of long-term steroids • Use of Low-dose Aspirin • Use of Calcium ($> 1g/24h$) • Use of Eicosapentaenoic acid (fish oil) $> 2,7g$ • Use of Vit. C $\geq 1000mg$ & Vit. E ≥ 400 UI • Use of Heparin/LMW Heparin • Untreated Thyroid disease • Use of antidepressant and/or anxiolytic agents

* All information regarding fetal anomalies will be properly recorded

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Table 3. Measurement frequency and maximum return periods according to gestational age – MAES I

Gestational age	Measurement frequency	Maximum return period (weeks)
19 – 32 weeks	20Hz	4
33 – 36 weeks	30Hz	2
37 – 42 weeks	50Hz	1

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Table 4. Performance of wrist and hip actigraphy methods according to different activities

	Hip			Wrist		
	Sens	Spec	BA	Sens	Spec	BA
Sitting	0.894	0.923	0.908	0.883	0.870	0.876
Vehicle	0.870	0.987	0.929	0.823	0.964	0.893
Walking/running	0.687	0.981	0.834	0.574	0.983	0.779
Standing	0.797	0.929	0.851	0.687	0.904	0.795
Average	0.812	0.955	0.881	0.742	0.930	0.836

BA: balanced accuracy; sens: sensitivity; spec: specificity

Adapted from Ellis K *et al.* Hip and Wrist Accelerometer Algorithms for Free-Living Behavior Classification. *Med. Sci. Sports Exerc.* 2016.

Table 5. Severe Neonatal Morbidity definition according to term/preterm status

Preterm	Term
Grade III and IV intraventricular haemorrhage	Grade II or III hypoxic ischemic encephalopathy
Chronic lung disease (home on O ₂ or on O ₂ at 36 weeks gestation)	Ventilation>24 hours
Necrotizing enterocolitis	Neonatal intensive care admission >4 days
Retinopathy of prematurity, stage 3 or 4	Apgar score <4 at 5 mins
Sepsis (blood or CSF culture proven)	Cord arterial pH<7.0 and/or base excess>-15
Cystic peri-ventricular leukomalacia	Neonatal seizures

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3 **Figure legends:**
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6 **Figure 1.** Set points of MAES-I study

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8 **Figure 2.** Estimated prevalence of preterm birth and preeclampsia according to
9 gestational age (RED represents majority of cases) and period of evaluation of PA and
10 sleep patterns (in GREY)
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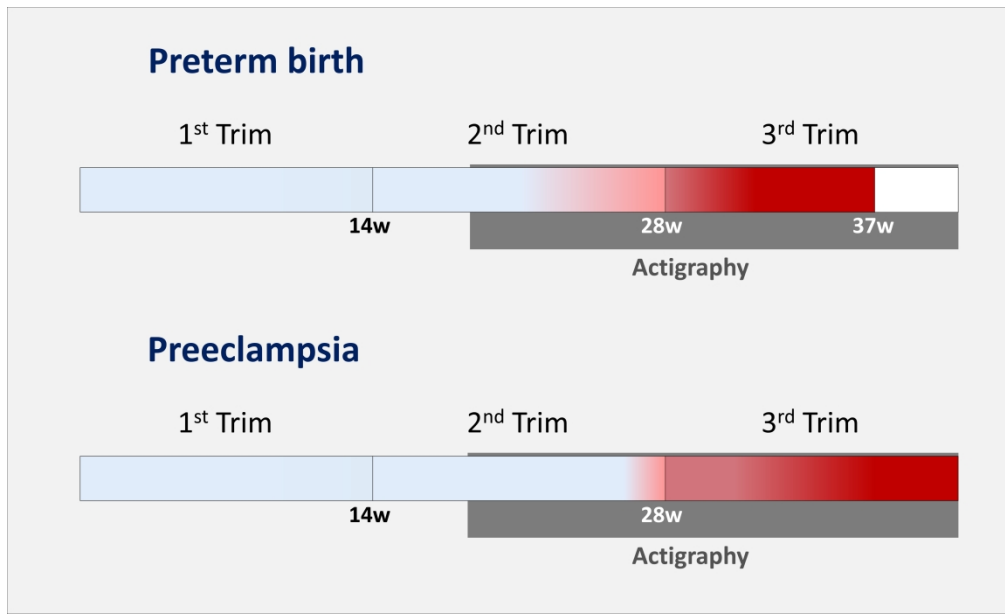


Figure 1

402x244mm (300 x 300 DPI)

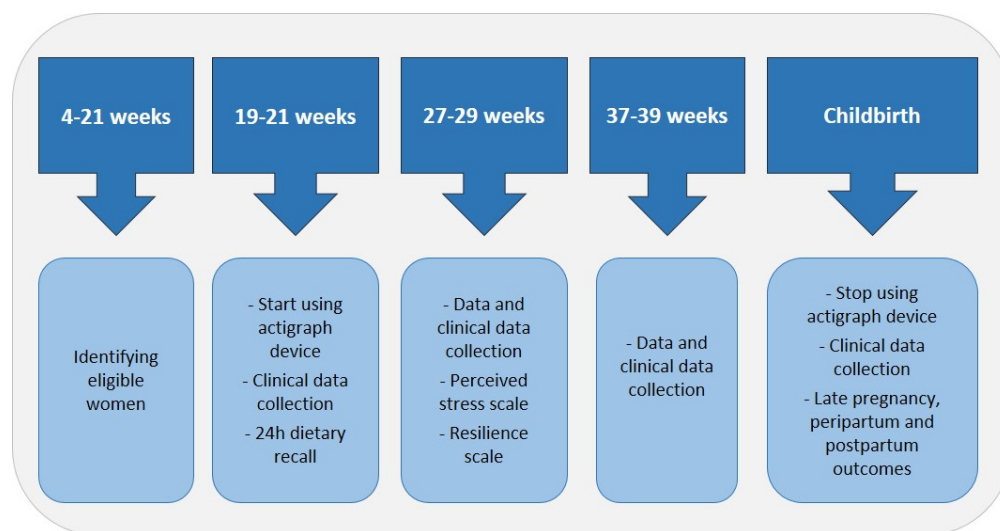


Figure 2

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	1,2,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7,8
		(b) <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-15
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-15
Bias	9	Describe any efforts to address potential sources of bias	16,17
Study size	10	Explain how the study size was arrived at	15
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	16,17
		(b) Describe any methods used to examine subgroups and interactions	16,17
		(c) Explain how missing data were addressed	17
		(d) <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	n/a
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	n/a
			n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	7,8
			n/a
Outcome data	15*	<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	n/a
			n/a
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
			n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	17
Discussion			
Key results	18	Summarise key results with reference to study objectives	n/a
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The identification of earlier predictors of pregnancy complications through wearable technologies in a Brazilian multicenter cohort: Maternal Actigraphy Exploratory Study I (MAES-I) study protocol

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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	wearable technologies, actigraph, physical activity, sleep patterns, pregnancy complications

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STUDY PROTOCOL

The identification of earlier predictors of pregnancy complications through wearable technologies in a Brazilian multicenter cohort: Maternal Actigraphy Exploratory Study I (MAES-I) study protocol

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1 **Abstract**

2 **Introduction:** Non-invasive tools capable of identifying predictors of maternal
3 complications would be a step forward in the improvement of maternal and perinatal
4 health. There is association between modification of physical activity (PA) and sleep-
5 wake patterns and the occurrence of inflammatory, metabolic, pathologic conditions as
6 chronic diseases. The actigraph device is validated to estimate PA and sleep-wake
7 patterns among pregnant women. In order to extend the window of opportunity to
8 prevent, diagnose and treat specific maternal conditions, would it be possible to use
9 actigraphic data to identify risk factors for the development of adverse maternal
10 outcomes during pregnancy?

11 **Methods and analysis:** A cohort will be held in 5 centres from the Brazilian Network for
12 Studies on Reproductive and Perinatal Health. MAES-I will enroll 400 low-risk nulliparous
13 women that will wear the actigraph device on the wrist during day and night (24h/day)
14 uninterruptedly from 19-21 weeks until childbirth. Changes in PA and sleep-wake
15 patterns through pregnancy will be analyzed, considering gestational age ranges, in
16 women with and without maternal complications during pregnancy, such as
17 preeclampsia, preterm birth (spontaneous or provider-initiated), gestational diabetes,
18 maternal haemorrhage and also perinatal outcomes. A predictive model for screening
19 pregnant women at risk of presenting specific adverse maternal and perinatal outcomes
20 is planned to be developed using the actigraphy data.

21 **Ethics and Dissemination:** MAES-I study has been reviewed and approved by each
22 Institutional Review Board (IRB) and also by the National Council for Ethics in Research.
23 Detailed information of the study is provided in the Brazilian Cohort website
24 (www.medscinet.com/samba) and findings will be publicized in scientific literature and
25 Institutional webpages.

26 **Keywords:** wearable technologies; actigraph; physical activity; sleep patterns; sleep-
27 wake cycle; prediction; pregnancy complications.

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1 **Strengths and limitations of this study**

- 2 • This multicentre cohort will collect comprehensive data on the main maternal
3 and perinatal complications as pre-eclampsia, small for gestational age/fetal
4 growth restriction, preterm birth and gestational diabetes mellitus.
- 5 • Physical activity and sleep patterns will be estimated through an innovative
6 wearable device used in the natural environment of the study subject.
- 7 • Physical activity and sleep patterns will be estimated from the beginning of the
8 second half of pregnancy until delivery, covering a wide interval during
9 pregnancy and enabling the study of PA and sleep patterns changes throughout
10 pregnancy.
- 11 • One possible limitation refers to the uncovered first half of pregnancy regarding
12 this information.

1 **Background**

2 Reducing the global maternal mortality ratio to less than 70 per 100,000 live births by
3 2030 is one of the targets of the new United Nations Sustainable Development Goals
4 [1]. Multiple challenges need to be tackled to achieve this target, but the 2016-2030
5 health and development agenda goes well beyond mortality reduction. The Global
6 Strategy for Women's, Children's and Adolescent's Health aims to ensure that every
7 newborn, women and child not only survive but thrive. This will only be possible if a
8 transformative agenda, with innovation at the central stage, is put into action [2].

9 One of the major challenges that need to be addressed is optimizing the recognition of
10 earlier predictors and identifiers of maternal and perinatal complications. Delays in
11 diagnosing and managing maternal complications have been associated with poor
12 outcomes [3]. The reduced self-perception of clinical signs related to maternal
13 complications, difficulties in accessing the health system and poor quality of care may
14 contribute to the late identification of complications and worsened prognosis. The
15 development of a non-invasive Antenatal Care (ANC) tool capable of identifying
16 maternal sub-clinical signs during pregnancy may provide the window of opportunity for
17 the earlier identification of abnormal patterns of physiologic parameters related to
18 pregnancy complications. We consider earlier identification when the recognition could
19 be made before clinical presentation, when standard criteria based on clinical signs,
20 symptoms, and supplementary tests are presented. Shortening the time between the
21 onset of a complication and the initiation of the appropriate management allow for
22 secondary prevention and reduction of maternal morbidity and mortality [3–7].

23 Pervasive computing (i.e. the trend towards embedding microprocessors in everyday-
24 life objects so they can generate data) and wearable technology (i.e. clothing and
25 accessories incorporating computer and advanced electronic technologies such as wrist
26 and/or waistband sensors) are ubiquitous and able to generate a new dataset that needs
27 to be correlated with pregnancy outcomes. Preterm birth and preeclampsia, for
28 instance, are two important pregnancy complications that have a relatively long
29 subclinical phase before the appearance of signs or symptoms [8, 9]. It is plausible that
30 during this subclinical phase of certain conditions the pattern of physical activity (PA) or
31 sleep-wake rhythm is affected in some way and this change could be captured through

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3 1 wearable devices. Although some studies show that PA patterns (actigraphy
4 parameters) may be related to systemic inflammation and diseases in the general
5 population [10, 11], published literature correlating wearable technology data and
6 maternal complications are very scarce.
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11 5 The human circadian rhythm is ruled by endogenous physiologic mechanisms and
12 environmental stimuli [12]. There is solid evidence showing that modification of
13 circadian rhythm or sleep and PA patterns are an underlying condition related to
14 inflammatory, degenerative and/or metabolic chronic diseases as diabetes,
15 hypertension, and cancer [13]. Circadian misalignment is defined as having
16 inappropriate timed sleep and wake, misplaced feeding periods and modification of
17 activity behavior.
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24 12 The determination of cause or consequence effect between these modifications and the
25 development of pathological conditions is a complex task. It seems that changes in
26 appetite-stimulating hormones, glucose metabolism, inflammatory markers, and mood
27 are some of the related pathways [13–15]. Leproult *et al.* evaluated the effect of
28 circadian misalignment on metabolic and inflammation markers in cardiovascular
29 disease [15]. The insulin action and release, and also the levels of some inflammatory
30 markers that are predictors for cardiovascular diseases, were abnormal in individuals
31 with circadian misalignment. The mechanisms involved in the association between
32 changes of PA pattern and pathologic conditions seem to be of multiple etiologies. Sani
33 *et al.* assessed the circadian rhythm of more than 2,300 African descendant adults. More
34 than evaluating physical activity itself, the authors aimed to identify chronobiologic
35 patterns of adults from different socioeconomic settings. The study identified that
36 chronobiologic behavior can vary depending on individual BMI, socioeconomic
37 background, work type and time of sunlight exposure. Possibly, many other factors are
38 involved in modifications of chronobiologic behavior, such as pathologic conditions.
39 Some metabolic, cognitive, cardiovascular and other chronic degenerative diseases have
40 been associated with particular patterns of PA and sleep [10, 11, 16–18]. A previous
41 observational study assessed various sleep parameters during pregnancy, e.g. sleep
42 onset latency (SOL), wake after sleep onset (WASO) and total nocturnal sleep time (TST).
43 Difficulty in initiating sleep in early pregnancy was associated with higher body mass
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1 index, greater weight gain and higher blood pressure during pregnancy [17]. Palagini *et*
2 *al.* reviewed clinical evidence between chronic sleep loss and pregnancy adverse
3 outcomes, discussing common mechanisms of stress system activation [19]. Low-quality
4 evidence suggests an association between sleep loss and prenatal depression,
5 gestational diabetes, preeclampsia, abnormal length of labour, caesarean delivery,
6 abnormal fetal growth, and preterm birth. Those results corroborate with other findings
7 regarding pregnancy and sleep disorders [20–23].

8 The assessment of PA and the sleep patterns can be performed using small wrist (or
9 waist) devices similar to a regular watch (actigraphy technology). The type of sensor,
10 batteries, materials and output data have been substantially developed in recent years,
11 enabling low cost, comfort, discretion and performance [24]. Nowadays there are
12 devices that are portable, lightweight and with a large capacity to storage information,
13 including a software with automatic scoring algorithms packages for the detection of
14 wakefulness, sleep periods and PA [24, 25]. The actigraphy estimation of PA and sleep
15 patterns is validated as a proxy for chronobiologic behavior [26–29] and 7 to 14 days
16 using the actigraph device provides reliable estimates of PA behavior in older adults [30–
17 32]. Both hip and wrist devices show reliable and acceptable performance in estimating
18 PA and sleep-wake patterns [33–36].

19 The main advantages of using wearable devices for actigraphy is the non-invasiveness,
20 24/7 monitoring of the circadian pattern and PA, and informing sleep habits and
21 parameters in the user natural environment [24, 25, 28]. We propose an innovative and
22 strategic approach to monitor PA and sleep-wake patterns during pregnancy,
23 establishing a large database comprised of clinical, epidemiological, PA and sleep-wake
24 variables potentially capable of composing a prediction model for maternal
25 complications during pregnancy. The main goal of this study is to identify earlier
26 predictors of pregnancy complications by correlating data generated on PA and sleep
27 patterns through wearable devices (wristband sensors) with maternal and perinatal
28 complications and outcomes.

29 **Methods/Design**

30 ***Study design***

1 We will conduct a cohort study of 400 pregnant women using wrist sensor bands able
2 to capture information on daily physical activity and sleep patterns (exposure). This
3 cohort study will be implemented in 5 ANC clinics linked to obstetric units in 3 different
4 regions of Brazil that are already part of the Brazilian Network for Studies on
5 Reproductive and Perinatal Health [37], as shown in Table 1. During a period of eight
6 months, the ANC clinics will identify eligible cases for using the wristband sensors.
7 Wearable technology data will be correlated with the occurrence of pregnancy and
8 childbirth complications and outcomes, such as hypertensive disorders, gestational
9 diabetes mellitus, fetal growth restriction and prematurity.

10 Eligible women will be identified up to 21 weeks of gestation and invited to participate.
11 A proper consent form will be applied and the women who agree to participate will
12 receive a wristband sensor to be used starting at 19-21 weeks until childbirth,
13 uninterruptedly.

14 ***Study setting and population***

15 Brazil is a multi-ethnic mixed-race population of diverse resourced settings [38]. Despite
16 the considered high global overall human development index (HDI 0.727) in 2010, the
17 HDI of Brazilian municipalities ranged from 0,862 to 0,418 [39]. The possibility of
18 considering such mixed population is suitable to explore information regarding maternal
19 patterns of mobility and sleep, maximizing external validity and comparisons to other
20 populations. The following reasons support the study population being focused in low-
21 risk nulliparous women: 1) Previous obstetric history can refer to known risk factors for
22 many maternal complications such as preterm birth, preeclampsia, and diabetes [13,
23 40]. Therefore nulliparous women enable unbiased sampling regarding obstetric history.
24 2) Women with previous morbidity such as hypertension, diabetes, nephropathy or
25 others chronic/degenerative diseases are more likely to present abnormalities of sleep-
26 wake rhythm or physical activity patterns during pregnancy.

27 ***Sampling***

28 The five participating centers are regional referral obstetric units responsible for
29 antenatal care assistance mainly for high-risk pregnant women. Participating centers are
30 listed in Table 1. Nevertheless, there are primary health care units strategically linked

1 with these participating centers, enabling the identification and enrollment of women
2 with non-pathological pregnancies. The recruitment strategies include approaching all
3 eligible women in these participating centers and their linked facilities. An informed
4 consent form will be applied for women who agree to participate.

5 *Eligible women: Low-risk pregnant subjects*

6 There is no international consensus on the criteria for low-risk pregnancies, although
7 there are several known factors associated with maternal and perinatal adverse
8 outcomes. A recent study evaluating complications of “low-risk” pregnancies of US
9 Americans (10 million births from 2011 through 2013) showed that 29% of low-risk
10 women had an unexpected complication requiring no routine obstetric/neonatal care
11 [41]. This shows the difficulty in establishing a “low-risk profile” for maternal/perinatal
12 complications. In order to better identify eligible low-risk pregnant women, we excluded
13 potential known confounders of pre-pregnancy conditions that could be related to
14 adverse maternal or perinatal outcomes as shown in Table 2, so we could assess PA and
15 sleep patterns of a mostly “normal” population. Nonetheless, lifestyle habits and body
16 composition (Body mass index, height, etc.) characteristics, and some non-severe
17 chronic diseases as non-severe anaemia and/or asthma are not among the exclusion
18 criteria in this study but may be part of subgroup analyses (composition of any previous
19 disorder, e.g.). Intra and inter-individual analyses of PA and sleep patterns enable the
20 identification of potential confounders affecting primary outcomes, avoiding potential
21 biases. It means that comparison of PA and sleep pattern parameters collected in
22 different stages of pregnancy from the same participant (intra-individual analysis) and
23 collected at the same stage of pregnancy from different participants (inter-individual
24 analysis) will be carried out.

25 Eligible women will be enrolled between 04-21 weeks. The inclusion and exclusion
26 criteria are presented in Table 2.

27 **Data collection methods**

28 Essentially, MAES I study is comprised of 4 key set points – 3 clinical visits during
29 pregnancy and a postnatal visit. The clinical visits will be held at 1) between 19-21 weeks;
30 2) between 27-29 weeks; 3) between 37-39 weeks. At first, second, third and postnatal

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3 1 visits, additional information regarding maternal history, details on pregnancy
4 2 complications, maternal biophysical data (weight, height, skinfolds) and pregnancy
5 3 adverse outcomes will be collected following a specific Standard Operating Procedure
6 4 (SOP) specially developed for MAES-I study. Additionally, the Perceived Stress Scale [42]
7 5 and Resilience Scale [43] will be applied during 27-29w visit. Figure 1 shows the set
8 6 points of MAES-I study.

9 7 Eligible women will be invited to use a 43mmx40mmx13mm water-resistant wrist device
10 8 similar to a regular watch (GENEActiv Original – Activinsights®). The device contains
11 9 accelerometer to estimate PA and sensors to estimate sleep-wake patterns through light
12 10 and temperature measurements, using a proper software algorithm.

13 11 At the first set point of MAES-I study (between 19+0 - 21+0 weeks of gestation), eligible
14 12 women who agreed to participate will be instructed that the wrist bracelet device should
15 13 be worn on the non-dominant arm during day and night (24h/day) uninterruptedly until
16 14 childbirth (including bathing or aquatic activities). The participant will not have to press
17 15 any button or take any special care regarding the functioning of the device, which will
18 16 be configured to register physical activity and sleep-wake data automatically from the
19 17 moment it is delivered at the antenatal care visit. Also the battery charge will be held by
20 18 the research assistant before delivering the device to the participant woman.

21 19 The acquisition of actigraphy data can be performed in different frequencies (from 10Hz
22 20 to 100Hz). Since the frequency of data acquisition impacts on the battery life of the
23 21 device (inverse relationship), the measurement frequency will be set up according to
24 22 the participant's gestational age (Table 3). This information will be registered in the
25 23 database accordingly. The data accumulated will be downloaded during participant's
26 24 antenatal care visits, according to the maximum return periods showed in Table 3. The
27 25 maximum return periods were calculated taking into consideration the expected battery
28 26 life. At each antenatal care visit, the used device will be returned to the research team
29 27 and a new charged device will be provided to the participant.

30 28 A leaflet with detailed information and FAQ (Frequently asked questions) on the device
31 29 will also be provided to the women. They will also have a cell phone number to call
32 30 whether doubts arise regarding the procedures for using the device, or if any technical
33 31 or medical concern arises.

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3 1 During each antenatal care visit, the wrist device will be connected to a charge base
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5 2 which can be connected to a computer through an USB connection. All actigraphy data
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7 3 will be extracted to the computer as a raw data “.bin” file. An open source proper
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9 4 software (Geneactiv Software®) will allow to convert this file into “.csv” compressed
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11 5 epoch files for each 30 minutes of registered data, which can be read in Excel® program.
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13 6 Then, the actigraphy data will be uploaded to an online database platform developed by
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15 7 MedSciNet®, where all clinical data of the study will also be registered.

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17 8 The actigraphy software uses several algorithms to translate numerical information
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19 9 obtained through the epoch files into physical activity and sleep-wake patterns, which
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21 10 will compose the independent variables of this study. The database is centralized,
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23 11 secure, internet-based and allows several procedures for prospective and retrospective
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25 12 monitoring, hierarchical access (local user, general manager, etc.). The database will be
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27 13 translated into Portuguese and English, facilitating data collection for Portuguese-
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29 14 speaking team and international monitoring. A correspondent paper form will be
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31 15 available for data collection if necessary (e.g. internet connection failure for instance).

32 *Decision to start monitoring PA and sleep patterns between 19-21weeks*

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34 17 There are various underlying mechanisms involved in the development of the maternal
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36 18 and perinatal adverse outcomes that will be assessed, as preterm birth, preeclampsia,
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38 19 gestational diabetes, fetal growth restriction and small for gestational age. The pre-
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40 20 clinical phase, stage where there are no clinical signs or symptoms, might be different
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42 21 for each disease and dependent on environmental and individual aspects. The study of
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44 22 adverse maternal and perinatal predictors has been focused in early pregnancy so far
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46 23 (first trimester, <14 weeks of gestation), aiming to maximize the window of opportunity
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48 24 for preventative interventions. However, we hypothesized that the modification of PA
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50 25 and/or sleep pattern due to maternal underlying changes of biological function might
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52 26 not be evident at a very early stage in pregnancy before the beginning of the pre-clinical
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54 27 phase. Our hypothesis is that it possibly occurs shortly before symptoms.

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56 28 Additionally, we took into account that the occurrence of the main maternal
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58 29 complications, as preeclampsia, fetal growth restriction, and preterm birth, are more
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60 30 common in late pregnancy to establish the period between 19-21 weeks as appropriate
31 to start the assessment of PA and sleep patterns. A recent cross-sectional study

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3 1 conducted in 20 referral centres in Brazil, including the five participating centres of this
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5 2 proposal, showed that the occurrence of preterm birth before 28 weeks comprised less
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7 3 than 1% of all births and less than 8% of all preterm births [44]. In addition, the early
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9 4 onset of preeclampsia (before 34 weeks of gestation) complicates less than 0.4% of all
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11 5 pregnancies, according to a large retrospective cohort of more than 450,000 deliveries
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13 6 in USA [45]. Figure 2 outlines the predicted prevalence of preterm birth and
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15 7 preeclampsia in the second trimester, highlighting its clinical presentation, when classic
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17 8 symptoms and signs of a certain disease/complication are presented, through
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19 9 pregnancy in red. Our hypothesis is that PA and sleep patterns might be altered closely
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21 10 to the clinical presentation, still in preclinical phase when there is no symptoms or signs.

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23 11 In brief, as an exploratory study, we indeed needed to make an arbitrary decision
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25 12 regarding interval of monitoring PA and sleep patterns. For that, we had taken into
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27 13 consideration: 1) the main maternal/perinatal complications of interest occur in the
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29 14 second half of pregnancy, more precisely in late pregnancy (Figure 2); 2) we hypothesize
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31 15 that any potential change on PA or sleep patterns might occur days or weeks before the
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33 16 onset of maternal or perinatal complication. Then, we focused monitoring women
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35 17 during second half of pregnancy.

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37 18 Thus, the start of assessment between 19-21 weeks seems to be very reasonable,
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39 19 providing a wide interval to monitor and predict the main maternal and perinatal
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41 20 adverse outcomes.

41 *Actigraph device*

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43 22 The actigraph device that will be used to monitor PA and sleep-wake patterns is
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45 23 GENEActiv Original (GENEActiv, Activinsights Ltd, Huntingdon, UK). The device has
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47 24 multiple sensors as microelectromechanical (MEMS) accelerometer, temperature
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49 25 (linear active thermistor) and light (silicon photodiode), providing crude raw data for a
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51 26 variety of applications.

52 53 27 *Wrist vs waist wear: advantages and performance*

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55 28 Wrist wear of actigraph devices provides more comfortable use during wake and sleep
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57 29 periods and highest wear time compared to waist monitors [33, 46]. A non-systematic
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59 30 review published in 2011 showed that actigraphy is a useful and reliable tool to assess
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3 1 sleep patterns and circadian rhythm disorders, although there are some limitations on
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5 2 diagnosing sleep diseases or measuring sleep stages [25]. Actigraphy showed excellent
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7 3 concordance with polysomnography in assessing sleep parameters in healthy subjects
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9 4 (sensitivity >90% in estimating total sleep time, for instance). A recent study evaluated
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11 5 the concordance of physical activity estimation of wrist device in free-living settings in
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13 6 forty overweight or obese women [34]. They used both wrist and hip devices, and a
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15 7 small camera that captured participant behaviour for 7 days, enabling the monitoring of
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17 8 physical activity behaviour (gold-standard comparison). The hip and wrist machine
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19 9 learning (ML) classifiers used are different due to the different methods/algorithms to
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21 10 estimate physical activity [34]. The sensitivity and specificity of hip and wrist estimations
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23 11 according to Ellis *et al* are showed in Table 4 [34].

24
25 12 Two years ago, the same author had published a similar evaluation using 40 adults
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27 13 (women and men), showing that the hip and wrist accelerometers obtained an average
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29 14 accuracy of 92.3% and 87.5%, respectively, in predicting PA types [47].

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31 15 Staudenmayer *et al* developed an investigation with 20 participants also using two
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33 16 devices (wrist- and hip- worn), and showed that wrist actigraphy can estimate energy
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35 17 expenditure accurately and relatively precisely [48]. Another study evaluating PA
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37 18 patterns in a free-living environment with wrist devices showed that women in the top
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39 19 40% or bottom 40% of the distribution of daily PA, hip and wrist accelerometers agreed
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41 20 on the classification for about 75% of the women [49]. Additionally, the total activity
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43 21 (counts per day) was moderately correlated (Spearman's $r = 0.73$) between the wrist
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45 22 and hip worn devices.

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47 23 At the best of our knowledge, there are no systematic reviews or other high-quality
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49 24 evidence-based recommendation supporting a particular method. Although wrist wear
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51 25 of actigraphy is not the more traditional method, it might be the best choice for
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53 26 assessing long periods of PA or sleep patterns, even more considering the similar
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55 27 performance of the waist wear. The current proposal does not intend to diagnose
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57 28 pathologic behaviours or diseases, but to identify different patterns along pregnancy
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59 29 and in different subgroups of women. Therefore, supported by the evidence that wrist
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30 wear of actigraphy devices can accurately and more comfortably estimate PA and sleep

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3 1 patterns, mainly for long periods and in the free-living environment, the MAES-I study
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5 2 group adopted wrist wear devices.

6 3 **Main variables**

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10 4 The independent variables assessed as potential predictors of maternal complications
11
12 5 will be related to sleep-wake cycle and mobility as:

13 6 *“Sleep” variables*

- 14 7 - Sleep onset latency (SOL): time elapsed between full wakefulness to sleep.
- 15 8 - Total sleep time (TST): The amount of actual sleep time in a sleep episode (excludes
16 9 awakes).
- 17 10 - Wake after sleep onset (WASO): defined as total amount of time awake after sleep.
- 18 11 - Sleep Efficiency (SE): the proportion of sleep in the period potentially filled by sleep-
19 12 ratio of total sleep time to time in bed.

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28 13 The actigraph device collects many pieces of information related to body position and
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30 14 body movements to estimate the described sleep variables. Then, actigraphy software
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32 15 will be used to analyse the data and generate the output variables.

33 16 *“Physical activity” variables*

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36 17 Actigraphy technology estimates physical activity through various parameters
37
38 18 collected by the actigraph device. Briefly, according to Freedson *et al*, the triaxial
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40 19 sensors stressed by acceleration forces can estimate the intensity of movements. The
41
42 20 acceleration signal is converted to digital signal and summed over a user specified time
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44 21 interval (epoch). At the end of each epoch the activity count is stored. Then, according
45
46 22 to Count per minute (CPM) cut points, the PA intensity can be categorized [50]. The
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48 23 information is translated by the software using proper algorithms into quantitative
49
50 24 variables as following:

- 51 25 - Sedentary time (hours/day): the number of hours per day of count per minute
52 26 between 0-99.
 - 53 27 - Light activity (hours/day): the number of hours per day having count per minute
54 28 between 100 - 1951.
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- 1 - Moderate activity (minutes/day): the number of hours per day having count per
2 minute between 1952 - 5724.
- 3 - Vigorous activity (minutes/day): the number of hours per day having count per
4 minute between 5725 - 9498.
- 5 - Very vigorous activity (minutes/day): the number of hours per day having count
6 per minute between 9499 - ∞ .
- 7 - MET rates: Metabolic Equivalents (METs) are commonly used to also express the
8 intensity of physical activities. One MET is the energy cost of resting quietly, often
9 defined in terms of oxygen uptake as $3.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. MET rate expresses a
10 person's working metabolic rate relative to their resting metabolic rate. Briefly,
11 the triaxial piezoelectric sensors stressed by acceleration forces can estimate the
12 intensity of movements, converted to the oxygen consumption required to
13 perform such movement.
- 14 - Step counts/day: estimated steps count per day (estimated by proper algorithms
15 using accelerometer data.)

16 *Outcomes*

17 The primary outcomes are late pregnancy complications as:

- 18 - Preeclampsia: Hypertension after 20 weeks of gestation, systolic BP $\geq 140\text{mmHg}$
19 and/or diastolic BP $\geq 90\text{mmHg}$ (Korotkoff V) on at least 2 occasions 4h apart with:
20 1) Proteinuria 300 mg/24h or spot urine protein: creatinine ratio 30 mg/mmol
21 creatinine or urine dipstick protein $\geq (+)$ OR, in the absence of proteinuria,
22 hypertension and 2) any multi-system complication that are: Haematological
23 abnormalities; thrombocytopenia (platelets $< 100 \times 10^9/\text{L}$); Disseminated
24 intravascular coagulation (DIC), and haemolysis; Liver disease: increased aspartate
25 transaminase and/or alanine transaminase $> 45 \text{ IU/L}$ and/or severe right upper
26 quadrant or epigastric pain, liver rupture; Neurological problems: eclampsia,
27 imminent eclampsia (severe headache with hyperreflexia and persistent visual
28 disturbance), cerebral haemorrhage; Acute renal insufficiency: new increase in
29 serum creatinine to $> 100 \text{ mmol/L}$ antepartum or $> 130 \text{ mmol/L}$ postpartum;
30 Pulmonary oedema confirmed by chest x-ray [51].

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3 1 - Gestational Diabetes: new diabetes developing in pregnancy according to the WHO
4 recommendation [52] that defines gestational diabetes as having:
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7 3 ○ Fasting plasma glucose \geq 92 mg/dl, or
8 ○ 1-h plasma glucose tolerance test (75g load) \geq 180 mg/dl, or
9 ○ 2-h plasma glucose tolerance test (75g load) \geq 153 mg/dl.
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12 6 - Spontaneous Preterm Birth: spontaneous onset of preterm labour or premature
13 rupture of membranes leading to preterm birth, childbirth before 37 weeks of
14 gestation.
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17 9 - Provider-Initiated Preterm Birth: defined as childbirth occurring at less than 37
18 weeks, medically indicated due to maternal/fetal compromise or both;
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21 11 - Maternal Hemorrhage: Classified in 1) Antepartum haemorrhage defined as
22 bleeding from the genital tract after 24 weeks of gestation; 2) Primary Postpartum
23 haemorrhage as the loss of 500 ml blood or more from the genital tract within 24
24 hours of the childbirth.
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29 Secondary outcomes include childbirth variables and neonatal adverse outcomes as
30 fetal death, caesarean section, small for gestational age (defined as birth weight below
31 percentile 10 for gestational age), Apgar score $<$ 7 at 5 minutes, neonatal severe
32 morbidity (Table 5) and neonatal mortality before discharge.
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36 **Plans for analyses**

37 *Sample size estimation*

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42 This is an exploratory and innovative study focused on a specific population (pregnant
43 women) and therefore there are no previously published parameters available for
44 sample size estimation. Considering a relatively wide range of frequency of
45 complications arising in pregnancy from 3 to 20% (including preeclampsia, fetal growth
46 restriction, gestational diabetes, hemorrhage, preterm birth, etc.), a theoretical large
47 population size (above 1 million pregnant women), an acceptable margin of error of 4%,
48 the involvement of 5 clusters (participating centers) and a 95% level of confidence, 384
49 women would be necessary. Therefore, we are rounding up this estimation for at least
50 400 initially low-risk pregnant women to be enrolled in the study. We estimated the
51 incidence of some main maternal complications considering the following studies:
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- 1 - Pre-eclampsia: An international prospective cohort study with nulliparous women called SCOPE used similar criteria for the low-risk profile, having 5% of incidence of pre-eclampsia [53].
- 2 - Preterm Birth: A recent cross-sectional study conducted in 20 referral obstetric centres in Brazil, including the five participant centres of this proposal, showed a prevalence of 12.3% of all births [44].
- 3 - Gestational Diabetes: SCOPE international cohort, previously mentioned, had a prevalence of 8.9% of gestational diabetes in low-risk screened nulliparous women, according to mainly to the NICE guidelines [54].
- 4 - Fetal growth restriction/small for gestational age: SCOPE international cohort, previously mentioned, had a prevalence of 10.7% of newborns small for gestational age, according to the customized centiles of birthweight (<10%)[55].

13 *Statistical Analysis details*

14 According to these studies above, the predicted incidence of these complications seems reasonable and reproducible in our cohort. Then, sample size estimation might assure enough cases of maternal and perinatal complications for the current proposal.

17 The epoch files obtained from Geneactv Software by reading data of sleep variables and physical activity parameters will be translated into numerical results and then averaged in periods of 7 days. By doing this, there will be one value to be used in statistical analysis for each variable per week of use of the wrist device.

21 Firstly, we will identify PA and sleep-wake patterns of women who did not develop adverse maternal or perinatal outcomes. It will permit the recognition of a normal PA and sleep-wake patterns in low-risk population without complication during pregnancy. Using the same population, we will analyze changes in PA and sleep-wake patterns through pregnancy, allowing for gestational age periods.

26 Then, we will compare the PA and sleep-wake patterns of women who developed specific adverse maternal or perinatal outcomes with those who did not. The differences between groups might be identified to be used as potential markers for specific pregnancy complications.

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2
3 1 After that, we will analyze changes in PA and sleep-wake patterns of women who
4 developed adverse maternal or perinatal outcomes through pregnancy, comparing the
5 patterns and trying to discover which changes and when before the onset it would be
6 related to pregnancy complications. If possible, we will conduct subgroup analysis
7 including subpopulation with potential higher risk for maternal complications
8 (confounder variables), including obesity, smoking, etc.

9 Finally, we will develop a predictive model for screening pregnant women for risk of
10 specific adverse maternal and perinatal outcomes using PA and sleep-wake data
11 estimated with actigraphy technology.

12 The analysis will be performed using the actigraph software that translates the collected
13 information into PA and sleep-wake parameters. Additionally, data regarding time of
14 sleep onset latency, wake after sleep onset and total sleep time as well as sleep
15 efficiency will be compared between participants along the whole pregnancy time using
16 Friedman and Wilcoxon for paired samples. ANOVA and t-test will be used to compare
17 the sleep parameters between the participants for each week of gestational age for
18 repeated measures. The same tests will be applied to analyze quantitative data
19 regarding the median of number of hours per day having different types of physical
20 activity (sedentary, light, moderate, vigorous and very vigorous), MET rates and
21 estimative os steps/day through the entire gestational period examined, and the
22 comparison between the participants for each week of gestational age. Also, we will
23 address sensitivity, specificity and likelihood ratio for altered PA and sleep patterns or
24 for their changes throughout pregnancy.

25 ***Discontinuation of participants***

26 The criteria for discontinuation include:

- 27 - Withdrawal of consent;
- 28 - Not regularly using the actigraph device for long periods, less than 50% of all planned
29 time. The information that they are not using the device properly will be recorded if
30 women notice the MAES-I team. Otherwise, the low use of the device will be noticed
31 after data discharge during antenatal care visits.
- 32 - The loss to follow-up, not allowing the download of actigraphy data.

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3 1 Those women who decide to leave follow-up will be asked by telephone call to return
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5 2 the wrist device and a last visit will be set in order to regain the wrist monitor and direct
6
7 3 the woman to a proper antenatal care service to continue their consultations.
8

9 4 **Data and Sample Quality**

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11 5 All entered data will be prospectively and retrospectively monitored by local research
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13 6 assistants and a global monitor. Internal consistency of variables will be constantly
14
15 7 performed by the database and error messages are automatically flagged. A local
16
17 8 research assistant will be responsible for checking all forms and actigraphy data before
18
19 9 locking forms, assuring good quality of data (double-checking entered data and checking
20
21 10 for inconsistencies between variables, for instance). Then, the local principal
22
23 11 investigator (PI) will be responsible for signing the case, enabling its incorporation to the
24
25 12 final database. The University of Campinas will coordinate, implement and monitor the
26
27 13 study in the five participating centres. A general manager and a global monitor are also
28
29 14 part of the team of the coordinating centre. The local team of each participating centre
30
31 15 is comprised of a Local PI and research assistants.

32 16 **Ethics and Dissemination**

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34 17 MAES-I study focuses on low-risk nulliparous Brazilian pregnant women. Despite being
35
36 18 considered of low risk for maternal and perinatal complications, they are not free of
37
38 19 suffering complications. Furthermore, the first and second delays, defined as a delay in
39
40 20 deciding to seek care and delay in reaching a health care facility [56], are not uncommon,
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42 21 establishing a barrier between earlier recognition of symptoms and timely interventions
43
44 22 capable to successfully treat potentially life-threatening conditions. We believe that
45
46 23 women will feel encouraged, empowered and willing to participate in the study that
47
48 24 aims to develop a potentially useful prenatal care tool to identify the risk for maternal
49
50 25 and perinatal morbidity and mortality. Following national ethical regulations, the
51
52 26 participants will not receive any financial compensation.

53
54 27 Women who agree to participate in the study will not have any disadvantages or
55
56 28 compromise of their prenatal care. On the contrary, they will receive a telephone
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58 29 number to contact the clinical researchers at any time (24/7 service), which enables a
59
60 30 closer contact with researchers and providers of care, since the MAES-I team are

1 committed to contacting providers of care if any potential complication is noticed by
2 participants.

3 The participating women will not be responsible if loss, theft or damage to the wrist
4 device occurs. They will be asked only to use the device just as a regular wrist-watch
5 would be worn and no self-damage is expected in those who use it.

6 Participating women will not be able to identify any PA or sleep parameters at any stage
7 of the study. The download of the data is only possible through the own licensed
8 software of the device. Actigraphy devices provided for participating women have a
9 unique code which will be recorded in the database together with the interval of use for
10 each women. Actigraphy data will be labelled using participant ID, device number,
11 gestational age when starting using each device and return date of each device. The use
12 of such codes, ID`s and numbers will ensure confidential identify for all participating
13 women. The identity of all women will be kept confidential.

14 MAES-I study has been reviewed and approved by the National Committee for Ethics in
15 Research of Brazil (CONEP) and by the Institutional Review Board (IRB) of the
16 coordinating centre (Letter of approval 1.834.116 issued on 24th November 2016) and
17 of all other Brazilian participating centres. All women who will be enrolled in the MAES-I
18 cohort will sign an informed consent form.

19 The ethical principles stated in the Brazilian National Health Council (Resolution CNS
20 466/12) will be respected in every stage of this study. The anonymity of the source of
21 information will be guaranteed and the care for the women will be provided
22 independently of her agreement to participate in the study. The study also complies with
23 the Declaration of Helsinki amended in Hong Kong in 1989. The methodological and
24 ethical aspects of MAES-I study protocol were developed following STROBE guidelines
25 [57].

26 *Patient and Public Involvement*

27 Patients and public were not involved in this study for the development of the research
28 question and outcome measures. However, the choice for a wrist device was based on
29 the preference of users as reported. Participants of the study will have access to the
30 results by its webpage that will be open access.

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3 1 Detailed information of the study is provided in the Brazilian Cohort website
4 (www.medscinet.com/samba) and findings will be publicized in scientific literature and
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7 3 Institutional webpages. We intend to disseminate our findings in scientific peer-
8
9 4 reviewed journal, general free access website, specialists' conferences, and to our
10
11 5 funding agencies.
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15 7 **Discussion**

17 8 The actigraphy is an innovative, non-invasive, non-operator dependent, wearable
18
19 9 technology, which enables the estimative under real life conditions of diverse variables
20
21 10 related to mobility, physical activity, sleep-wake, and circadian cycle patterns. Actigraph
22
23 11 devices show high sensitivity in sleep-wake parameters detection and are currently
24
25 12 highly recommended by the American Sleep Disorder Association for diagnosis and
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27 13 therapy response of circadian rhythm disorders [27, 28, 58]. Although some studies
28
29 14 show that 7 to 14 days using the actigraph device provides reliable estimates of physical
30
31 15 activity behavior in older adult, it is not absolutely clear how many days is needed to
32
33 16 estimate habitual PA by using the wrist/waist device during pregnancy. In general, it
34
35 17 seems to depend mainly on the type of actigraph device, position of wear and target
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37 18 population [30, 33]. Nevertheless, MAES-I study will provide sufficient data to assess
38
39 19 different patterns along pregnancy.

40 20 The use of wearable physical activity monitors has grown enormously due to the interest
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42 21 about the relationship between the pathophysiology of diseases and physical activity
43
44 22 and sleep patterns. A recent study on the use of physical activity monitors in human
45
46 23 physiology research unravels the current and potential uses of actigraph device as in
47
48 24 strategies to promote healthier behaviour or to predict outcomes [59]. The authors
49
50 25 conclude that physical activity monitors, as others new 21st century technologies, have
51
52 26 already transformed physiology research, revolutionizing the way we assess patients and
53
54 27 opening new areas of interest. In addition, the use of objectives measures to evaluate
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56 28 habitual sleep duration and outcomes in pregnancy is critical, taking into account recent
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58 29 investigations reporting little agreement between objective and subjective assessments
59
60 30 of sleep time [60].

1 Alterations in sleep patterns, as less deep sleep and more nocturnal awakenings, can be
2 observed in pregnancy as early as 10-12 weeks gestation [61]. Sleep disturbances during
3 pregnancy have been associated with preterm delivery, gestational hypertensive
4 disorders, glucose intolerance and increased risk of caesarean delivery [19]. Shorter
5 night time sleep was also associated with hyperglycemia [62]. Persistent sleep deficiency
6 is correlated with depressive symptoms and stress perception by pregnant women [61].
7 These studies lay correlation between PA patterns and sleep disturbances determining
8 complications, in a well-established relationship of cause and consequence, although
9 sometimes it could not be adequately determined due to the study design [17].

10 In a distinct way, our analysis intends to figure out if the maternal complication could be
11 identified by physical activity and/or sleep patterns modifications, even during its pre-
12 clinical period, previous the appearance of clinical signs. Considering the existing
13 evidence, we speculate that the PA and/or sleep patterns change days or weeks before
14 the clinical presentation of the complication. In general, the signs and symptoms of some
15 maternal outcomes are part of the gold-standard criteria for diagnosis (high blood
16 pressure, proteinuria and/or edema in the case of preeclampsia; premature contractions
17 and cervical ripening/dilation in preterm birth; abnormal placental blood flow and
18 insufficient fetal growth in Intrauterine Growth Restriction). We acknowledge the fact
19 that there are potential confounders and limitations in predicting maternal and perinatal
20 complications using PA and sleep patterns estimated by actigraph devices. We expect
21 that our studied population will have different subgroups of women with different risks
22 and associated factors playing a role on maternal complication. It includes obesity,
23 smoking, extremes of age, for instance. None of those factors was considered exclusion
24 criteria and, if possible, we intend to assess subgroup analysis for those maternal
25 subgroups at they might present different PA and sleep patterns. Nonetheless, we
26 decided to perform a pragmatic approach, not excluding such common factor from our
27 sample.

28 The use of actigraph device during prenatal visits has a potential to become a new tool
29 to monitor pregnant women, improving maternal health care, identifying altered PA
30 and/or sleep patterns, measured objectively through actigraphy, before the occurrence
31 of those signs and symptoms. Therefore, the focus would be offering new technology to

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1 monitor the development of a potential maternal complication. Other positive points of
2 our study are the period of data collection (from 19 weeks till delivery) and the low-risk
3 profile of the cohort. Through which, it would be possible to describe a PA and sleep
4 patterns in a low-risk pregnant population and better interpret actigraphy data among
5 pregnant women. The current clinical and biological predictors for the main maternal
6 complications as preeclampsia, preterm birth, maternal haemorrhage, and gestational
7 diabetes still lack for effective sensitivity and specificity.

8 If this is confirmed to be true, an important step will be achieved for a possible
9 introduction of screening non-invasive procedures during prenatal care with the
10 purpose of identifying women at higher risk of developing those conditions. Therefore,
11 they could receive specific orientation on prevention and earlier detection of the onset
12 of condition for taking immediate action to look for professional health care and
13 receiving appropriate interventions, avoiding delays that are the most striking factor for
14 the low quality of care the women usually receive in low and middle-income settings,
15 contributing to the still high burden of maternal morbidity and mortality. If we were
16 successful in identifying such “specific patterns of physical activity and sleep” as
17 predictors for pregnancy complications, further validation studies will necessarily be
18 recommended for assessing its effectiveness for the whole management of such
19 conditions. Additionally, MAES-I will enable further specific studies among high risk
20 population and also will help to identify the best gestational age for monitoring, giving
21 the means to target a specific gestational age interval.

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1 Abbreviations

ANC – antenatal care	min – minutes
BMI – body mass index	mg – milligram
BP – blood pressure	mL – millilitre
CPM – count per minute	mmol – millimole
dL – decilitre	NICE – National Institute for Health and Care Excellence
FAQ – frequently asked questions	PA – physical activity
h – hour	PI – Principal investigator
HDI – human development index	SE – sleep efficiency
Hz - hertz	SCOPE – SCReening Of Pregnancy Endpoints
Kg – kilogram	SOL – sleep onset latency
L – litre	TST – total nocturnal sleep time
MAES-I – maternal Actigraphy Exploratory Study I	US – United States
MEMS – microelectromechanical	USA – United States of America
MET – metabolic equivalent	w – week
METs – metabolic equivalents	

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the overall study design and specific methodologies. RTS, JGC, JM, MLC and JPS conceived the study design and wrote the first version of the study protocol. In a first meeting, the protocol was discussed and incorporated suggestions from RBG, FEF, ERF, DFL, JV, RPT and DSS. RTS, JGC, JM, and RBG planned the implementation of the study and developed the necessary material. RTS, JM, MLC and JGC drafted the manuscript that was afterwards revised by all other authors who gave suggestions. All authors discussed and made important contributions to the manuscript, read and approved the final version for submission.

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Table 1. Participating centers in the Maternal Actigraphy Exploratory Study I (MAES-I)

<ul style="list-style-type: none"> • The Maternity of CAISM, University of Campinas, in Campinas, SP, Brazil; <ul style="list-style-type: none"> ○ Local Principal Investigator: Maria Laura Costa.
<ul style="list-style-type: none"> • Maternity of the Clinic Hospital, Federal University of RS, Porto Alegre, RS, Brazil; <ul style="list-style-type: none"> ○ Local Principal Investigator: Janete Vettorazzi.
<ul style="list-style-type: none"> • Maternity of the University Hospital, Jundiaí Medical School in Jundiaí, SP, Brazil; <ul style="list-style-type: none"> ○ Local Principal Investigator: Ricardo Porto Tedesco.
<ul style="list-style-type: none"> • Maternity of Clinic Hospital, Federal University of Pernambuco, in Recife, PE, Brazil; <ul style="list-style-type: none"> ○ Local Principal Investigator: Edilberto A Rocha Filho.
<ul style="list-style-type: none"> • MEAC – School Maternity of the Federal University of Ceará, in Fortaleza, CE, Brazil. <ul style="list-style-type: none"> ○ Local Principal Investigator: Francisco Edson de Lucena Feitosa.

Table 2. Inclusion and Exclusion Criteria of MAES – I

Inclusion Criteria	
• Singleton pregnancy	
• Nulliparous (who had never given birth before)	
• Between 19+0 – 21+0 weeks of gestation	
Exclusion Criteria	
• Unsure LMP and unwilling to have to date the Ultrasound	• Major Uterine Anomaly
• ≥ 3 Miscarriages	• Cervical Suture
• Major Fetal Anomaly/Abnormal Karyotype*	• Knife cone biopsy
• Essential Hypertension Treated Pre-pregnancy	• Ruptured membranes
• Mod-Severe Hypertension at booking ($\geq 160/100$ mmHg) or Chronic hypertension using antihypertensive medication	• Use of long-term steroids
• Pre-pregnancy Diabetes	• Use of Low-dose Aspirin
• Renal Disease	• Use of Calcium ($> 1g/24h$)
• Systemic Lupus Erythematosus	• Use of Eicosapentaenoic acid (fish oil) $> 2,7g$
• Anti-phospholipid Syndrome	• Use of Vit. C $\geq 1000mg$ & Vit. E ≥ 400 UI
• Sickle Cell Disease	• Use of Heparin/LMW Heparin
• HIV or Hep B or Hep C positive	• Untreated Thyroid disease
• Any condition that limits practice of physical activity	• Use of antidepressant and/or anxiolytic agents

* All information regarding fetal anomalies will be properly recorded

Table 3. Measurement frequency and maximum return periods according to gestational age – MAES I

Gestational age	Measurement frequency	Maximum return period (weeks)
19 – 32 weeks	20Hz	4
33 – 36 weeks	30Hz	2
37 – 42 weeks	50Hz	1

Table 4. Performance of wrist and hip actigraphy methods according to different activities

	Hip			Wrist		
	Sens	Spec	BA	Sens	Spec	BA
Sitting	0.894	0.923	0.908	0.883	0.870	0.876
Vehicle	0.870	0.987	0.929	0.823	0.964	0.893
Walking/running	0.687	0.981	0.834	0.574	0.983	0.779
Standing	0.797	0.929	0.851	0.687	0.904	0.795
Average	0.812	0.955	0.881	0.742	0.930	0.836

BA: balanced accuracy; sens: sensitivity; spec: specificity

Adapted from Ellis K *et al.* Hip and Wrist Accelerometer Algorithms for Free-Living Behavior Classification. *Med. Sci. Sports Exerc.* 2016.

Table 5. Severe Neonatal Morbidity definition according to term/preterm status

Preterm	Term
Grade III and IV intraventricular haemorrhage	Grade II or III hypoxic ischemic encephalopathy
Chronic lung disease (home on O ₂ or on O ₂ at 36 weeks gestation)	Ventilation>24 hours
Necrotizing enterocolitis	Neonatal intensive care admission >4 days
Retinopathy of prematurity, stage 3 or 4	Apgar score <4 at 5 mins
Sepsis (blood or CSF culture proven)	Cord arterial pH<7.0 and/or base excess>-15
Cystic peri-ventricular leukomalacia	Neonatal seizures

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3 **Figure legends:**
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6 **Figure 1.** Set points of MAES-I study
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8 **Figure 2.** Estimated prevalence of preterm birth and preeclampsia according to
9 gestational age (RED represents majority of cases) and period of evaluation of PA and
10 sleep patterns (in GREY)
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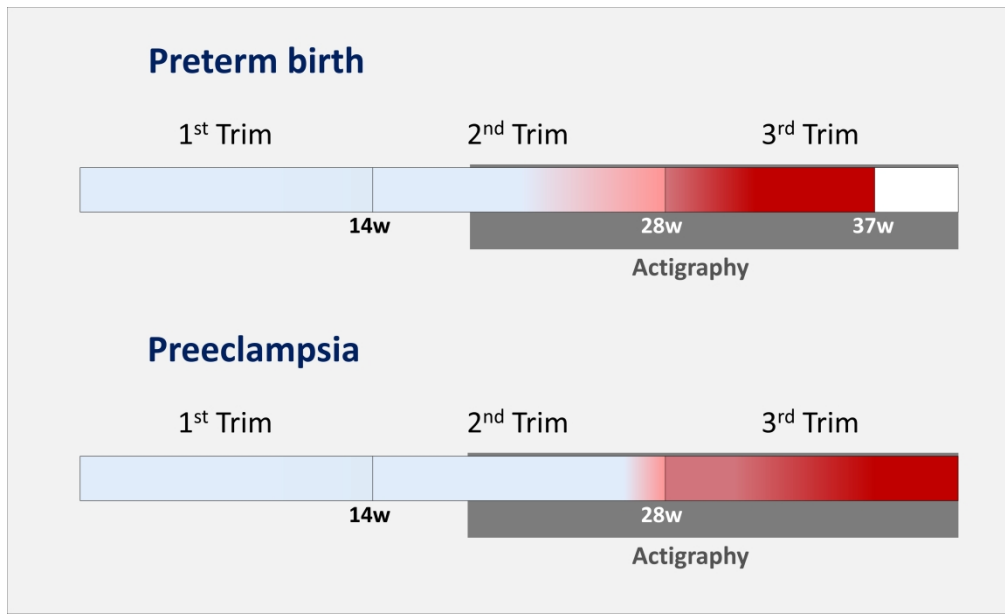


Figure 1

402x244mm (300 x 300 DPI)

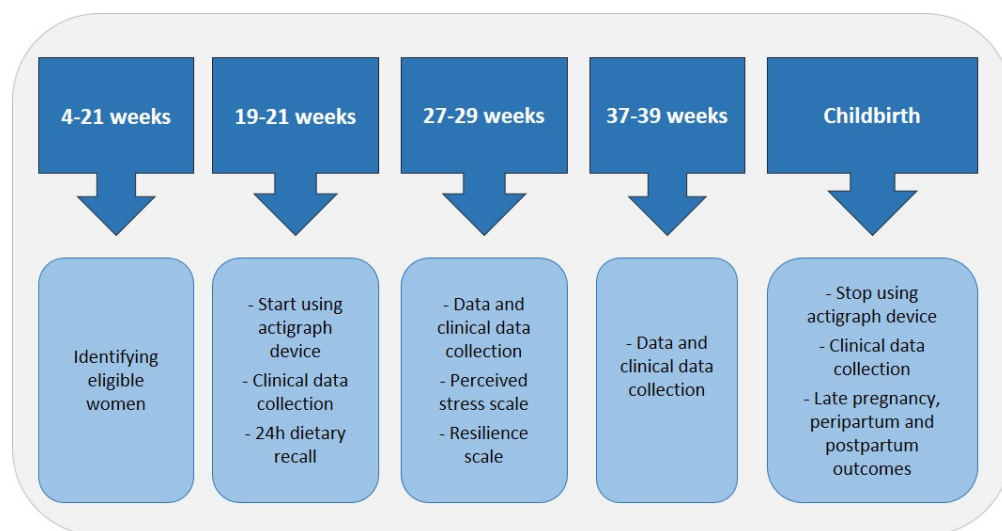


Figure 2

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	1,2,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7,8
		(b) <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-15
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-15
Bias	9	Describe any efforts to address potential sources of bias	16,17
Study size	10	Explain how the study size was arrived at	15
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	16,17
		(b) Describe any methods used to examine subgroups and interactions	16,17
		(c) Explain how missing data were addressed	17
		(d) <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	n/a
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	n/a
			n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	7,8
			n/a
Outcome data	15*	<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	n/a
			n/a
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
			n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	17
Discussion			
Key results	18	Summarise key results with reference to study objectives	n/a
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The identification of earlier predictors of pregnancy complications through wearable technologies in a Brazilian multicenter cohort: Maternal Actigraphy Exploratory Study I (MAES-I) study protocol

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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	wearable technologies, actigraph, physical activity, sleep patterns, pregnancy complications

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STUDY PROTOCOL

The identification of earlier predictors of pregnancy complications through wearable technologies in a Brazilian multicenter cohort: Maternal Actigraphy Exploratory Study I (MAES-I) study protocol

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1 **Abstract**

2 **Introduction:** Non-invasive tools capable of identifying predictors of maternal
3 complications would be a step forward for improving maternal and perinatal health.
4 There is an association between modification in physical activity (PA) and sleep-wake
5 patterns and the occurrence of inflammatory, metabolic, pathologic conditions related
6 to chronic diseases. The actigraphy device is validated to estimate PA and sleep-wake
7 patterns among pregnant women. In order to extend the window of opportunity to
8 prevent, diagnose and treat specific maternal conditions, would it be possible to use
9 actigraphy data to identify risk factors for the development of adverse maternal
10 outcomes during pregnancy?

11 **Methods and analysis:** A cohort will be held in 5 centres from the Brazilian Network for
12 Studies on Reproductive and Perinatal Health. MAES-I will enroll 400 low-risk nulliparous
13 women who will wear the actigraphy device on their wrists day and night (24h/day)
14 uninterruptedly from 19-21 weeks until childbirth. Changes in PA and sleep-wake
15 patterns will be analysed throughout pregnancy, considering ranges in gestational age
16 in women with and without maternal complications such as preeclampsia, preterm birth
17 (spontaneous or provider-initiated), gestational diabetes, maternal haemorrhage during
18 pregnancy, in addition to perinatal outcomes. The plan is to design a predictive model
19 using actigraphy data for screening pregnant women at risk of developing specific
20 adverse maternal and perinatal outcomes.

21 **Ethics and Dissemination:** MAES-I study has been reviewed and approved by each
22 Institutional Review Board (IRB) and also by the National Council for Ethics in Research.
23 Detailed information about the study is provided in the Brazilian Cohort website
24 (www.medscinet.com/samba) and findings will be published in the scientific literature
25 and Institutional webpages.

26 **Keywords:** wearable technologies; actigraphy; physical activity; sleep patterns; sleep-
27 wake cycle; prediction; pregnancy complications.

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1 **Strengths and limitations of this study**

- 2 • This multicentre cohort will collect comprehensive data on major maternal and
3 perinatal complications such as pre-eclampsia, small for gestational age/fetal
4 growth restriction, preterm birth and gestational diabetes mellitus.
- 5 • Physical activity and sleep patterns will be estimated by an innovative wearable
6 device used in the natural environment of the study subject.
- 7 • Physical activity and sleep patterns will be estimated from the beginning of the
8 second half of pregnancy until delivery, covering a wide interval during
9 pregnancy, allowing for the study of changes in PA and sleep patterns
10 throughout pregnancy.
- 11 • One possible limitation is the first half of pregnancy at a time when this
12 information was not covered.

1 **Background**

2 Reducing the global maternal mortality ratio to less than 70 per 100,000 live births by
3 2030 is one of the targets of the new United Nations Sustainable Development Goals
4 [1]. Multiple challenges need to be tackled to achieve this target, but the 2016-2030
5 health and development agenda goes well beyond mortality reduction. The aim of the
6 Global Strategy for Women's, Children's and Adolescent's Health is to ensure that every
7 newborn, woman, and child not only survives but thrives. This will only be possible if a
8 transformative agenda centered on innovation is put into action [2].

9 One of the major challenges lies in optimizing earlier predictors and identifiers of
10 maternal and perinatal complications. Delays in diagnosing and managing maternal
11 complications have been associated with poor outcomes [3]. Decreased self-perception
12 of clinical signs related to maternal complications, difficulties in accessing the health
13 system and poor quality of care may contribute to late identification of complications
14 and a worse prognosis. The development of a non-invasive Antenatal Care (ANC) tool
15 for identifying maternal sub-clinical signs during pregnancy may provide a window of
16 opportunity for an earlier identification of abnormal patterns of physiological
17 parameters related to pregnancy complications. Earlier identification occurs when
18 recognition is made before clinical presentation by standard criteria based on clinical
19 signs, symptoms, and supplementary tests. Shortening the time between the onset of a
20 complication and the initiation of appropriate management enables secondary
21 prevention and reduction of maternal morbidity and mortality [3–7].

22 Pervasive computing (i.e. the trend towards embedding microprocessors in everyday-
23 life objects so they can generate data) and wearable technology (i.e. clothing and
24 accessories incorporating computer and advanced electronic technologies such as
25 sensor wristbands and/or waistbands) are ubiquitous and can generate a new dataset
26 that requires correlation with pregnancy outcomes. Preterm birth and preeclampsia are
27 two important pregnancy complications that have a relatively long subclinical phase
28 before the appearance of signs or symptoms [8, 9]. It is plausible that during subclinical
29 phases of certain conditions the pattern of physical activity (PA) or sleep-wake rhythm
30 is affected in some way and wearable devices could capture these changes. Although
31 some studies have shown that PA patterns (actigraphy parameters) may be related to

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3 1 systemic inflammation and diseases in the general population [10, 11], there is a paucity
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5 2 of published literature that correlates wearable technology data with maternal
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7 3 complications.

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9 4 The human circadian rhythm is regulated by endogenous physiological mechanisms and
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11 5 environmental stimuli [12]. Solid evidence indicates that modification in circadian
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13 6 rhythm or sleep and PA patterns are underlying conditions related to inflammatory,
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15 7 degenerative and/or metabolic chronic diseases such as diabetes, hypertension, and
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17 8 cancer [13]. Circadian misalignment is defined as inappropriately timed sleep and wake,
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19 9 misplaced feeding periods and modification in physical activity behaviour.

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21 10 Determining a cause or effect relationship between these modifications and the
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23 11 development of pathological conditions is a complex task. It seems that changes in
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25 12 appetite-stimulating hormones, glucose metabolism, inflammatory markers, and mood
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27 13 are some of the related pathways [13–15]. Leproult *et al.* evaluated the effect of
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29 14 circadian misalignment on metabolic and inflammation markers in cardiovascular
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31 15 disease [15]. Insulin action and release, and also levels of some inflammatory markers
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33 16 that are predictors of cardiovascular disease, were abnormal in individuals with
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35 17 circadian misalignment. The mechanisms involved in the association between changes
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37 18 in PA pattern and pathologic conditions seem to have multiple etiologies. Sani *et al.*
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39 19 assessed circadian rhythms of more than 2,300 African adult descendants. In addition
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41 20 to the evaluation of physical activity itself, the aim of those authors was to identify
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43 21 chronobiological patterns of adults from different socioeconomic settings. The study
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45 22 described that chronobiological behaviour can vary depending on individual BMI,
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47 23 socioeconomic background, work type and time of sunlight exposure. Many other
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49 24 factors, such as pathologic conditions, may be potentially involved in a modification in
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51 25 chronobiological behaviour. Some metabolic, cognitive, cardiovascular and other
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53 26 chronic degenerative diseases have been associated with particular patterns of PA and
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55 27 sleep [10, 11, 16–18]. A previous observational study assessed various sleep parameters
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57 28 during pregnancy, e.g. sleep onset latency (SOL), wake after sleep onset (WASO) and
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59 29 total nocturnal sleep time (TST). Difficulty in initiating sleep in early pregnancy was
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30 associated with higher body mass index, greater weight gain and higher blood pressure
31 during pregnancy [17]. Palagini *et al.* reviewed the clinical evidence between chronic

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1 sleep loss and adverse pregnancy outcomes, discussing common mechanisms of stress
2 system activation [19]. Low-quality evidence suggests an association between sleep loss
3 and prenatal depression, gestational diabetes, preeclampsia, abnormal length of labour,
4 caesarean delivery, abnormal fetal growth, and preterm birth. Those results corroborate
5 with other findings regarding pregnancy and sleep disorders [20–23].

6 Assessment of PA and sleep patterns can be performed by wearing small wrist (or waist)
7 devices similar to a regular watch (actigraphy technology). More recently, substantial
8 advance has been made in types of sensors, batteries, materials and output data,
9 leading to lower cost, comfort, discretion and performance of the devices [24].
10 Nowadays, portable, lightweight devices have a large capacity to store data, including
11 software with automatic scoring algorithm packages for the detection of wakefulness,
12 sleep periods and PA [24, 25]. Actigraphy estimation of PA and sleep patterns is
13 validated as a proxy for chronobiological behaviour [26–29] and the use of an actigraphy
14 device for 7 to 14 days provides reliable estimates of PA behaviour in older adults [30–
15 32]. The performance of both hip and wrist devices has been shown to be reliable and
16 acceptable for estimating PA and sleep-wake patterns [33–36].

17 The main advantages of using wearable devices for actigraphy are non-invasiveness,
18 24/7 monitoring of PA and circadian patterns, and information about sleep habits and
19 parameters in the natural environment of the subject [24, 25, 28]. We propose an
20 innovative and strategic approach to monitor PA and sleep-wake patterns during
21 pregnancy, establishing a large database comprised of clinical, epidemiological, PA and
22 sleep-wake variables that are potentially capable of composing a prediction model for
23 maternal complications during pregnancy. The main goal of this study is to identify
24 earlier predictors of pregnancy complications by establishing a correlation between data
25 on PA and sleep patterns using wearable devices (sensor wristbands) and maternal and
26 perinatal complications and outcomes.

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1 **Methods/Design**

2 ***Study design***

3 We will conduct a cohort study of 400 pregnant women using sensor wristbands
4 capable of capturing information on daily physical activity and sleep patterns
5 (exposure). This cohort study will be implemented in 5 ANC clinics linked to obstetric
6 units in 3 different regions of Brazil that are already part of the Brazilian Network for
7 Studies on Reproductive and Perinatal Health [37], as shown in Table 1. During an 8-
8 month period, the ANC clinics will identify cases that are eligible to use the sensor
9 wristband. Wearable technology data will be correlated with the occurrence of
10 pregnancy and childbirth complications and outcomes, such as hypertensive
11 disorders, gestational diabetes mellitus, fetal growth restriction and prematurity.

12 Eligible women will be identified up to 21 weeks of gestation and invited to participate
13 in the study. A proper consent form will be applied and women who agree to participate
14 will receive a sensor wristband to wear continuously from 19-21 weeks until childbirth.

15 ***Study setting and population***

16 Brazil is a multi-ethnic mixed-race population of diverse resourced settings [38]. Despite
17 the high global overall human development index (HDI 0.727) in 2010, the HDI of
18 Brazilian municipalities ranged from 0,862 to 0,418 [39]. A mixed population is suitable
19 for exploring information on patterns of maternal mobility and sleep, maximizing
20 external validity and comparisons to other populations. The following reasons support
21 a study population of low-risk nulliparous women: 1) Previous obstetric history can refer
22 to known risk factors for many maternal complications such as preterm birth,
23 preeclampsia, and diabetes [13, 40]. Therefore, nulliparous women permit unbiased
24 sampling regarding obstetric history. 2) Women with previous morbidities such as
25 hypertension, diabetes, nephropathy or other chronic/degenerative diseases are more
26 likely to present abnormalities in sleep-wake rhythms or physical activity patterns during
27 pregnancy.

1 **Sampling**

2 The five participating centres are regional referral obstetric units responsible for
3 antenatal care of mainly high-risk pregnant women. Participating centres are listed in
4 Table 1. Nevertheless, there are primary health care units strategically linked to these
5 participating centres, enabling the identification and enrolment of women with non-
6 pathological pregnancies. Recruitment strategies include approaching all eligible
7 women in these participating centres and their linked facilities. An informed consent
8 form will be applied for women who agree to participate.

9 *Eligible women: Low-risk pregnant subjects*

10 There is a lack of international consensus on criteria for low-risk pregnancies, although
11 several factors are known to be associated with maternal and perinatal adverse
12 outcomes. A recent study evaluating complications of “low-risk” pregnancies of US
13 Americans (10 million births from 2011 to 2013) indicated that 29% of low-risk women
14 experienced an unexpected complication that required no routine obstetric/neonatal
15 care [41]. This illustrates the difficulty in establishing a “low-risk profile” for
16 maternal/perinatal complications. To make a better identification of eligible low-risk
17 pregnant women, we excluded known potential confounders of pre-pregnancy
18 conditions that could be related to adverse maternal or perinatal outcomes as shown in
19 Table 2, so we could assess PA and sleep patterns of a mostly “normal” population.
20 Nonetheless, features such as lifestyle habits and body composition (body mass index,
21 height), and some non-severe chronic diseases including non-severe anaemia and/or
22 asthma are not exclusion criteria in this study. However, these features and conditions
23 may be a part of subgroup analyses (composition of any previous disorder, e.g.). Intra
24 and inter-individual analyses of PA and sleep patterns can avoid possible bias by
25 identifying potential confounders that may affect primary outcomes. A comparative
26 analysis will be conducted, in which parameters of PA and sleep patterns will be
27 collected in different stages of pregnancy from the same participant (intra-individual
28 analysis) and compared to data collected at the same stage of pregnancy from different
29 participants (inter-individual analysis).

30 Eligible women are to be enrolled at 04-21 weeks of gestation. Inclusion and exclusion
31 criteria are shown in Table 2.

1

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3 **Data collection methods**

4 Essentially, MAES I study is comprised of 4 key set points – 3 clinical visits during
5 pregnancy and a postnatal visit. Clinical visits will be held at 1) 19-21 weeks; 2) 27-29
6 weeks; and 3) 37-39 weeks. On the first, second, third and postnatal visits, additional
7 information on maternal history, details of pregnancy complications, maternal
8 biophysical data (weight, height, skinfolds) and adverse pregnancy outcomes will be
9 collected following a specific Standard Operating Procedure (SOP) specially developed
10 for MAES-I study. Furthermore, the Perceived Stress Scale [42] and Resilience Scale [43]
11 will be applied during the 27-29 weeks visit. Figure 1 shows the set points of MAES-I
12 study.

13 Eligible women will be invited to use a 43mmx40mmx13mm water-resistant wrist device
14 similar to a regular watch (GENEActiv Original – Activinsights®). The device contains an
15 accelerometer for PA calculation and sensors for estimation of sleep-wake patterns by
16 light and temperature measurements, using a proper software algorithm.

17 At the first set point of MAES-I study (between 19+0 - 21+0 weeks of gestation), eligible
18 women who agreed to participate will be instructed to wear the wrist bracelet device
19 on the non-dominant wrist night and day (24h/day), uninterruptedly until childbirth
20 (including bathing or recreational water activities). Participants will not need to press
21 any buttons and functioning of the device requires no special care. The device will be
22 configured to register physical activity and sleep-wake data automatically from the
23 moment it is delivered to the participant during antenatal care visit. In addition, the
24 battery charge will be held by the research assistant before delivering the device to the
25 study participant.

26 The acquisition of actigraphy data can be performed in different frequencies (from 10Hz
27 to 100Hz). Since the frequency of data acquisition has an impact on battery life of the
28 device (inverse relationship), measurement frequency will be set according to
29 gestational age of the participant (Table 3). This information will be registered in the
30 database accordingly. Cumulative data will be downloaded during antenatal care visits,

1 according to maximum return periods shown in Table 3. Calculation of maximum return
2 periods will be based on expected battery life. At each antenatal care visit, the used
3 device will be returned to the research team and a new charged device will be provided
4 to the participant.

5 A leaflet with detailed information and FAQ (Frequently asked questions) about the
6 device will also be provided. Women will also have a cell phone number to call in case
7 of any doubts regarding use of the device, or if any technical or medical concern arises.

8 During each antenatal care visit, the wrist device will be connected to a charge base
9 which can be connected to a computer through an USB connection. All actigraphy data
10 will be extracted to the computer as raw data “.bin” file. A proper open source software
11 (Geneactiv Software®) will allow the conversion of this file into “.csv” compressed epoch
12 files for each 30 minutes of registered data, which can be read in Excel® program. The
13 actigraphy data will then be uploaded to an online database platform developed by
14 MedSciNet®, where all clinical study data will also be registered.

15 The actigraphy software uses several algorithms to translate numerical information
16 obtained from epoch files into physical activity and sleep-wake patterns, which will
17 compose the independent variables of this study. This is a centralized, secure, internet-
18 based database that allows several procedures for prospective and retrospective
19 monitoring, hierarchical access (local user, general manager, etc.). The database will be
20 translated into Portuguese and English, facilitating data collection for Portuguese-
21 speaking teams and international monitoring. A correspondent paper form will be
22 available for data collection if necessary (e.g. internet connection failure for instance).

23 *Decision to start monitoring PA and sleep patterns between 19-21weeks*

24 There are various underlying mechanisms involved in the development of maternal and
25 perinatal adverse outcomes that will be assessed, such as preterm birth, preeclampsia,
26 gestational diabetes, fetal growth restriction and small for gestational age. Each disease
27 may have a different pre-clinical phase, depending on environmental and individual
28 aspects. In this phase, there are no clinical signs or symptoms. So far, the study of
29 adverse maternal and perinatal predictors has been focused on early pregnancy (first
30 trimester, <14 weeks of gestation) to maximize the window of opportunity for the

1 performance of preventive interventions. However, we hypothesized that modifications
2 in PA and/or sleep pattern due to underlying changes in maternal biological function
3 might not be evident at a very early stage in pregnancy before the beginning of the pre-
4 clinical phase. Our hypothesis is that changes might occur shortly before the
5 manifestation of symptoms.

6 Furthermore, we took into account that major maternal complications, including
7 preeclampsia, fetal growth restriction, and preterm birth, occur more commonly in late
8 pregnancy and established the period between 19-21 weeks as an appropriate time to
9 start assessment of PA and sleep patterns. A recent cross-sectional study conducted in
10 20 referral centres in Brazil, including the five participating centres of this proposal,
11 showed that the occurrence of preterm birth before 28 weeks comprised less than 1%
12 of all births and less than 8% of all preterm births [44]. In addition, the early onset of
13 preeclampsia (before 34 weeks of gestation) complicates less than 0.4% of all
14 pregnancies, according to a large retrospective cohort of more than 450,000 deliveries
15 in the USA [45]. Figure 2 outlines the predicted prevalence of preterm birth and
16 preeclampsia in the second trimester. Clinical presentation, when classic symptoms and
17 signs of a certain disease/complication occur, is highlighted by pregnancy in red. Our
18 hypothesis is that alterations in PA and sleep patterns may occur closer to clinical
19 presentation, still in the preclinical phase when there are no symptoms or signs.

20 Briefly, an exploratory study required an arbitrary decision about the interval for
21 monitoring PA and sleep patterns. To that end, we considered that: 1) the main
22 maternal/perinatal complications of interest occur in the second half of pregnancy,
23 more precisely in late pregnancy (Figure 2); 2) any potential change in PA or sleep
24 patterns occurred hypothetically days or weeks before the onset of maternal or
25 perinatal complications. Then, we focused on monitoring women during the second half
26 of pregnancy.

27 Thus, starting assessment at 19-21 weeks seems to be quite reasonable, providing a
28 wide interval to monitor and predict major maternal and perinatal adverse outcomes.

29
30 *Actigraphy device*

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3 1 The actigraphy device that will be used for monitoring PA and sleep-wake patterns is the
4
5 2 GENEActiv Original (GENEActiv, Activinsights Ltd, Huntingdon, UK). The device has
6
7 3 multiple sensors including a microelectromechanical (MEMS) accelerometer,
8
9 4 temperature (linear active thermistor) and light (silicon photodiode) sensors, providing
10
11 5 crude raw data for a variety of applications.

6 *Wrist vs waist wear: advantages and performance*

7 Wrist-worn actigraphy devices are more comfortable to use during wake and sleep
8 periods and provide the highest wear time compared to waist-worn monitors [33, 46].

9 A non-systematic review published in 2011 showed that actigraphy is a useful and
10 reliable tool to assess sleep patterns and circadian rhythm disorders, although there are
11 some limitations in the diagnosis of sleep disorders or measurement of sleep stages [25].

12 Actigraphy had a very good concordance with polysomnography for assessment of sleep
13 parameters in healthy subjects (i.e., sensitivity >90% in estimating total sleep time). A
14 recent study evaluated the concordance of physical activity estimation by wrist device
15 in free-living settings in forty overweight or obese women [34]. Those women used both
16 wrist and hip devices, and a small camera that captured participant behaviour for 7 days,
17 monitoring physical activity behaviour (gold-standard comparison). There was a
18 difference in hip and wrist machine learning (ML) classifiers, resulting from different
19 methods/algorithms used to measure physical activity [34]. The sensitivity and
20 specificity of hip and wrist estimations according to Ellis *et al* are shown in Table 4 [34].

21 Two years previously, the same author published a similar evaluation of 40 adult women
22 and men, showing that hip and wrist accelerometers predicted types of PA with an
23 average accuracy of 92.3% and 87.5% respectively [47].

24 Staudenmayer *et al* investigated 20 participants who also wore two devices (wrist and
25 hip), and concluded that wrist actigraphy can estimate energy expenditure in an
26 accurate and relatively precise manner [48]. Another study evaluated PA patterns in
27 women at the top 40% or bottom 40% of the distribution of daily PA who wore wrist
28 devices in a free-living environment. There was agreement in classification between hip
29 and wrist accelerometers in about 75% of those women [49]. Additionally, total activity
30 (counts per day) was moderately correlated (Spearman's $r = 0.73$) with wrist-worn and
31 hip-worn devices.

1 To the best of our knowledge, there are no systematic reviews or other high-quality
2 evidence-based recommendations that support a particular method. Although a wrist-
3 worn actigraphy device is not the most traditional method, it might be the best choice
4 for assessment of prolonged periods of PA or sleep patterns, considering that it
5 performs similarly to a waist-worn device. The current proposal has no intention of
6 diagnosing pathological behaviours or diseases, but it plans to identify different patterns
7 throughout pregnancy and in different subgroups of women. Evidence suggests that
8 wrist-worn actigraphy devices can accurately and more comfortably estimate PA and
9 sleep patterns, mainly during prolonged periods and in free-living environments.
10 Therefore, the MAES-I study group adopted a wrist-worn device.

11 ***Main variables***

12 Independent variables assessed as potential predictors of maternal complications will
13 be related to the sleep-wake cycle and mobility as:

14 *“Sleep” variables*

- 15 - Sleep onset latency (SOL): time elapsed between full wakefulness and sleep.
- 16 - Total sleep time (TST): The amount of actual sleep time in a sleep episode (excluding
17 time awake).
- 18 - Wake after sleep onset (WASO): defined as total amount of time awake after sleep.
- 19 - Sleep Efficiency (SE): the ratio between total sleep time and time in bed.

20 The actigraphy device collects many pieces of information related to body position and
21 body movements to estimate the described sleep variables. The actigraphy software will
22 then be used to analyse data and generate output variables.

23 *“Physical activity” variables*

24 Actigraphy technology estimates physical activity through various parameters
25 collected by the actigraphy device. Briefly, according to Freedson *et al*, the triaxial
26 sensors stressed by acceleration forces can estimate movement intensity. The
27 acceleration signal is converted to a digital signal and summed over a user-specified
28 time interval (epoch). At the end of each epoch the activity count is stored. Then,
29 according to count per minute (CPM) cut points, PA intensity can be categorized [50].

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3 1 The software translates information into quantitative variables using appropriate
4 algorithms as follows:
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6
7 3 - Sedentary (hours/day): the number of hours per day when the count per minute
8 ranges from 0-99.
9
10
11 5 - Light activity (hours/day): the number of hours per day when the count per
12 minute ranges from 100 - 1951.
13
14
15 7 - Moderate activity (minutes/day): the number of hours per day when the count
16 per minute ranges from 1952 - 5724.
17
18
19 9 - Vigorous activity (minutes/day): the number of hours per day when the count per
20 minute ranges from 5725 - 9498.
21
22
23
24 11 - Very vigorous activity (minutes/day): the number of hours per day when the
25 count per minute is 9499 - ∞ .
26
27
28 13 - MET rates: Metabolic Equivalents (METs) are also commonly used to express the
29 intensity of physical activity. One MET is the energy cost of resting quietly, often
30 defined by oxygen uptake as $3.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. MET rate expresses the working
31 metabolic rate of subjects in comparison to their resting metabolic rate. Briefly,
32 the triaxial piezoelectric sensors stressed by acceleration forces can estimate
33 movement intensity, converted to oxygen consumption required to perform such
34 a movement.
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37 18
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41 20 - Step counts/day: estimated step counts per day (estimated by proper algorithms
42 using accelerometer data.)
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45 *Outcomes*

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48 23 Primary outcomes are late pregnancy complications such as:

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50 24 - Preeclampsia: Hypertension after 20 weeks of gestation, systolic BP $\geq 140\text{mmHg}$
51 and/or diastolic BP $\geq 90\text{mmHg}$ (Korotkoff V) on at least 2 occasions 4h apart with:
52
53 26 1) Proteinuria 300 mg/24h or spot urine protein: creatinine ratio $30 \text{ mg}/\text{mmol}$
54 creatinine or urine dipstick protein $\geq (+)$ OR, in the absence of proteinuria,
55
56 27 hypertension and 2) any multi-system complication that are: Haematological
57
58 28 abnormalities; thrombocytopenia (platelets $< 100 \times 10^9/\text{L}$); Disseminated
59
60 29

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3 1 intravascular coagulation (DIC), and haemolysis; Liver disease: increased aspartate
4 2 transaminase and/or alanine transaminase > 45 IU/L and/or severe right upper
5 3 quadrant or epigastric pain, liver rupture; Neurological problems: eclampsia,
6 4 imminent eclampsia (severe headache with hyperreflexia and persistent visual
7 5 disturbance), cerebral haemorrhage; Acute renal insufficiency: new increase in
8 6 serum creatinine to > 100 mmol/L antepartum or > 130 mmol/L postpartum;
9 7 Pulmonary oedema confirmed by chest x-ray [51].

10 8 - Gestational Diabetes: new diabetes developing in pregnancy according to the WHO
11 9 recommendation [52] that defines gestational diabetes as :

- 12 10 ○ Fasting plasma glucose \geq 92 mg/dl, or
- 13 11 ○ 1-h plasma glucose tolerance test (75g load) \geq 180 mg/dl, or
- 14 12 ○ 2-h plasma glucose tolerance test (75g load) \geq 153 mg/dl.

15 13 - Spontaneous Preterm Birth: spontaneous onset of preterm labour or premature
16 14 rupture of membranes leading to preterm birth, childbirth before 37 weeks of
17 15 gestation.

18 16 - Provider-Initiated Preterm Birth: defined as childbirth occurring at less than 37
19 17 weeks, medically indicated due to maternal/fetal compromise or both;

20 18 - Maternal Hemorrhage: Classified as 1) Antepartum haemorrhage defined as
21 19 bleeding from the genital tract after 24 weeks of gestation; 2) Primary Postpartum
22 20 haemorrhage defined as the loss of at least 500 ml blood from the genital tract
23 21 within 24 hours of childbirth.

24 22 Secondary outcomes include childbirth variables and neonatal adverse outcomes such
25 23 as fetal death, caesarean section, small for gestational age (defined as birth weight
26 24 below percentile 10 for gestational age), Apgar score < 7 at 5 minutes, neonatal severe
27 25 morbidity (Table 5) and neonatal mortality before discharge.

28 26 ***Plans for analyses***

29 27 *Sample size estimation*

30 28 This is an exploratory and innovative study focused on a specific population (pregnant
31 29 women) and therefore there are no previously published parameters available for
32 30 sample size estimation. Considering that the rate of pregnancy-related complications is
33 31 3 to 20% (including preeclampsia, fetal growth restriction, gestational diabetes,

1
2
3 1 hemorrhage, preterm birth, etc.), assuming a large population (above 1 million pregnant
4 women), an acceptable margin of error of 4%, involvement of 5 clusters (participating
5 centres) and a 95% level of confidence, the study would require 384 women. Therefore,
6 we rounded up this estimation to 400 initially low-risk pregnant women for enrolment
7 in the study. We estimated the incidence of some main maternal complications
8 considering the following studies:

- 9 - Pre-eclampsia: An international prospective cohort study with nulliparous women
10 termed SCOPE used similar criteria for low-risk profile, with a 5% of incidence of pre-
11 eclampsia [53].
- 12 - Preterm Birth: A recent cross-sectional study conducted in 20 referral obstetric
13 centres in Brazil, including the five participating centres, showed that preterm birth
14 was prevalent in 12.3% of all births [44].
- 15 - Gestational Diabetes: In the previously mentioned SCOPE international cohort, the
16 prevalence of gestational diabetes was 8.9% in screened low-risk nulliparous
17 women, according to the NICE guidelines [54].
- 18 - Fetal growth restriction/small for gestational age: the previously mentioned SCOPE
19 international cohort had a prevalence of 10.7% of small for gestational age
20 newborns, according to customized centiles of birthweight (<10%)[55].

21 *Details of Statistical Analysis*

22 According to the studies above, the predicted incidence of complications seems
23 reasonable and reproducible in our cohort. Therefore, sample size estimation may
24 ensure a sufficient number of cases of maternal and perinatal complications for the
25 current proposal.

26 The epoch files obtained from Geneactv Software by reading data on sleep variables and
27 physical activity parameters will be translated into numerical results and then averaged
28 in 7-day periods. Therefore, only one value will be employed in statistical analysis for
29 each variable per week of use of the wrist-worn device.

30 First, we will identify PA and sleep-wake patterns of women who did not develop
adverse maternal or perinatal outcomes. This will permit the recognition of normal PA
and sleep-wake patterns in a low-risk population without complications during

1 pregnancy. We will use the same population to analyse changes in PA and sleep-wake
2 patterns throughout pregnancy, allowing for gestational age periods.

3 Subsequently, we will compare PA and sleep-wake patterns of women who developed
4 specific adverse maternal or perinatal outcomes with those who did not have any
5 complications. Differences between groups may be identified and used as potential
6 markers for specific pregnancy complications.

7 Afterwards, we will analyse changes in PA and sleep-wake patterns of women who
8 developed adverse maternal or perinatal outcomes throughout pregnancy, comparing
9 patterns in an attempt to discover which changes occurred before the onset of
10 symptoms that could be related to pregnancy complications. If possible, we will conduct
11 a subgroup analysis including a subpopulation with a potentially higher risk for maternal
12 complications (confounder variables), including obesity, smoking, etc.

13 Finally, we will develop a predictive model for screening pregnant women at risk of
14 specific adverse maternal and perinatal outcomes using PA and sleep-wake data
15 estimated by actigraphy technology.

16 Analysis will be performed using the actigraphy software that translates collected
17 information into PA and sleep-wake parameters. In addition, sleep onset latency, wake
18 after sleep onset and total sleep time as well as sleep efficiency will be compared
19 between participants throughout pregnancy using the Friedman and Wilcoxon tests for
20 paired samples. The ANOVA and t-test will be used to compare sleep parameters
21 between participants per week of gestational age for repeated measures. The same
22 tests will be applied to analyse quantitative data on the median number of hours per
23 day that different types of physical activity (sedentary, light, moderate, vigorous and
24 very vigorous) are performed, MET rates and estimate of steps/day through the entire
25 gestational period examined, and the comparison between participants per week of
26 gestational age. Also, we will address the sensitivity, specificity and likelihood ratio for
27 altered PA and sleep patterns or for their changes throughout pregnancy.

28 ***Discontinuation of participants***

29 Criteria for discontinuation include:

- 30 - Withdrawal of consent;

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3 1 - Irregular use of the actigraphy device for prolonged periods, less than 50% of the
4 whole planned time. Information of improper use of the device will be recorded if
5 2 women notify the MAES-I team. Otherwise, the low level of use of the device will be
6 3 observed after data discharge during antenatal care visits.
7 4

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10 5 - Loss to follow-up, preventing us from downloading actigraphy data.
11
12

13 6 Women who decide to withdraw from follow-up care will be called by telephone and
14 7 asked to return the wrist device. The last visit will be scheduled to regain the wrist
15 8 monitor and direct the woman to a proper antenatal care service to continue medical
16 9 consultations.
17
18

19 20 21 **Data and Sample Quality** 22

23 11 All entered data will be prospectively and retrospectively monitored by local research
24 12 assistants and a global monitor. Internal consistency of variables will be constantly
25 13 performed by database and error messages are automatically flagged. A local research
26 14 assistant will be responsible for checking all forms and actigraphy data before locking
27 15 forms, assuring the good quality of data (i.e. double-checking entered data and checking
28 16 for inconsistencies between variables). The local principal investigator (PI) will be in
29 17 charge of signing the case, which will then be incorporated into the final database. The
30 18 University of Campinas will coordinate, implement and monitor the study in the five
31 19 participating centres. A general manager and a global monitor are also part of the
32 20 coordinating team. The local team of each participating centre is comprised of a Local PI
33 21 and research assistants.
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36 37 38 39 40 41 42 43 44 **Ethics and Dissemination** 45

46 23 MAES-I study focuses on low-risk nulliparous Brazilian pregnant women. Although
47 24 classified as low risk for maternal and perinatal complications, these women are not free
48 25 from suffering complications. Furthermore, first and second delays, defined as a delay
49 26 in deciding to seek care and delay in reaching a health care facility [56], are not
50 27 uncommon. A barrier is created between earlier recognition of symptoms and timely
51 28 intervention for the successful treatment of potentially life-threatening conditions. We
52 29 believe that women will feel encouraged, empowered and willing to participate in a
53 30 study aimed at developing a potentially useful prenatal care tool to identify the risk for
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3 1 maternal and perinatal morbidity and mortality. Following national ethical regulations,
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5 2 the participants will not receive any financial compensation.
6

7 3 Women who agree to participate in the study will not have any disadvantage or
8
9 4 difficulties in prenatal care. On the contrary, they will receive a contact number to find
10
11 5 clinical researchers at any time (24/7 service), maintaining a closer contact with
12
13 6 researchers and care providers. The MAES-I team is committed to contact health care
14
15 7 providers if any potential complication arises.
16

17 8 Participating women will not be held accountable for any loss, theft or damage to the
18
19 9 wrist device. These women will only be required to wear the device as a regular wrist-
20
21 10 watch and no self-damage is expected.
22

23 11 Participating women will not be able to identify any PA or sleep parameters at any stage
24
25 12 of the study. Data can only be downloaded through proper licensed software of the
26
27 13 device. The actigraphy devices provided to participating women have a unique code
28
29 14 which will be recorded in the database along with the interval of use per woman.
30
31 15 Actigraphy data will be labelled using participant ID, device number, gestational age
32
33 16 when the device was initially used and the return date of each device. Codes, ID number
34
35 17 and numbers will ensure confidentiality of all participating women. The identity of all
36
37 18 women will be kept confidential.
38

39 19 MAES-I study has been reviewed and approved by the National Committee for Ethics in
40
41 20 Research of Brazil (CONEP) and by the Institutional Review Board (IRB) of the
42
43 21 coordinating centre (Letter of approval 1.834.116 issued on 24th November 2016) and
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45 22 of all other Brazilian participating centres. All women enrolled in the MAES-I cohort will
46
47 23 sign an informed consent form.
48

49 24 Ethical principles of the Brazilian National Health Council (Resolution CNS 466/12) will be
50
51 25 upheld at every stage of this study. Anonymity of the source of information will be
52
53 26 guaranteed and the woman will receive care irrespective of her agreement to
54
55 27 participate in the study. The study also complies with the Declaration of Helsinki
56
57 28 amended in Hong Kong in 1989. Methodological and ethical aspects of MAES-I study
58
59 29 protocol were developed following STROBE guidelines [57].
60

1 *Patient and Public Involvement*

2 Patients and the public were not involved in this study for the development of the
3 research question and outcome measures. However, the choice of a wrist device was
4 based on user preference as reported. Participants of the study will have access to
5 information available at the open-access website.

6 Detailed information about the study is provided in the Brazilian Cohort website
7 (www.medscinet.com/samba). Publications of the results of the study can be found in
8 the scientific literature and Institutional webpages. We intend to disseminate our
9 findings to a scientific peer-reviewed journal, general free access website, specialist
10 conferences, and our funding agencies.

11

12 **Discussion**

13 Actigraphy is an innovative, non-invasive, non-operator dependent, wearable
14 technology, that is capable of measuring diverse variables related to mobility, physical
15 activity, sleep-wake, and circadian cycle patterns under real-life conditions. Actigraphy
16 devices have a high sensitivity in detecting sleep-wake parameters and are currently
17 highly recommended by the American Sleep Disorder Association for diagnosis and
18 therapy response of circadian rhythm disorders [27, 28, 58]. Although some studies
19 show that using the actigraphy device for 7 to 14 days provides reliable estimates of
20 physical activity behaviour in older adults, it is not absolutely clear how many days are
21 needed to estimate habitual PA by using the wrist/waist device during pregnancy. In
22 general, it seems to depend mainly on the type of actigraphy device, wear location and
23 target population [30, 33]. Nevertheless, MAES-I study will provide sufficient data to
24 assess different patterns throughout pregnancy.

25 The use of wearable physical activity monitors has increased considerably, owing to
26 interest in the relationship between the pathophysiology of diseases and patterns of
27 physical activity and sleep. A recent study on the use of physical activity monitors in
28 human physiology research unravels current and potential use of the actigraphy device.
29 The device can be applied in strategies that promote a healthier behaviour or predict
30 outcomes [59]. The authors conclude that physical activity monitors, as well as other

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3 1 new 21st century technologies, have already transformed physiology research,
4
5 2 revolutionizing how we assess patients and opening new areas of interest. In addition,
6
7 3 the use of objective measures to evaluate habitual sleep duration and outcomes in
8
9 4 pregnancy is critical, considering recent reports of little agreement between objective
10
11 5 and subjective assessments of sleep time [60].

12
13 6 Alterations in sleep patterns, including less deep sleep and more nocturnal awakenings
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15 7 can be observed in pregnancy as early as in 10-12 weeks gestation [61]. Sleep
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17 8 disturbances during pregnancy have been associated with preterm delivery, gestational
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19 9 hypertensive disorders, glucose intolerance and increased risk of caesarean delivery
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21 10 [19]. Shortened nocturnal sleep time was also associated with hyperglycemia [62].
22
23 11 Persistent sleep deprivation has been correlated with depressive symptoms and stress
24
25 12 perception by pregnant women [61]. These studies explored a correlation between PA
26
27 13 patterns and sleep disturbances that determine complications through a well-
28
29 14 established relationship between cause and effect. However, this correlation could not
30
31 15 always be adequately determined due to study design [17].

32
33 16 In a distinct manner, the intent of our analysis is to discover whether a maternal
34
35 17 complication can be identified before the manifestation of its clinical signs, by evaluating
36
37 18 physical activity and/or sleep patterns modifications of pregnant women. Considering
38
39 19 existing evidence, we speculate that patterns of PA and/or sleep change days or weeks
40
41 20 before clinical presentation of the complication. In general, the signs and symptoms of
42
43 21 some maternal outcomes are part of the gold-standard criteria for diagnosis (high blood
44
45 22 pressure, proteinuria and/or edema in preeclampsia; premature contractions and
46
47 23 cervical ripening/dilation in preterm birth; abnormal placental blood flow and
48
49 24 insufficient fetal growth in Intrauterine Growth Restriction). We acknowledge that there
50
51 25 are potential confounders and limitations in predicting maternal and perinatal
52
53 26 complications using PA and sleep patterns estimated by actigraphy devices. The
54
55 27 population in our research is expected to have different subgroups of women with
56
57 28 different risks and associated factors contributing to maternal complications, such as
58
59 29 obesity, smoking habit, and with age under twenty or over forty years old, for instance.
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30 None of those factors was considered an exclusion criterion. If possible, we intend to
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conduct a subgroup analysis of the maternal subgroups, since they may have different

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1 PA and sleep patterns. Nonetheless, we decided to adopt a pragmatic approach and not
2 exclude such a common factor from our sample.

3 The use of actigraphy device during prenatal visits has the potential to become a new
4 tool for monitoring pregnant women. It may improve maternal health care and identify
5 altered PA and/or sleep patterns. Changes can be objectively measured by actigraphy
6 before the occurrence of signs and symptoms. The focus is on providing new technology
7 to monitor the development of potential maternal complications. Other positive points
8 in our study are the data collection period (from 19 weeks until delivery) and the low-
9 risk profile of the cohort, enabling us to describe PA and sleep patterns in a low-risk
10 pregnant population and make a better interpretation of actigraphy data among
11 pregnant women. Current clinical and biological predictors of major maternal
12 complications such as preeclampsia, preterm birth, maternal haemorrhage, and
13 gestational diabetes still lack effective sensitivity and specificity.

14 If our hypothesis is confirmed, this will be an important step for introducing non-invasive
15 screening procedures into prenatal care to identify women at higher risk for those
16 conditions. Women could receive specific advice on the prevention and earlier detection
17 of the condition, take immediate action and seek professional health care to receive
18 appropriate treatment. This would avoid delays, the most significant factors
19 contributing to low-quality health care in underprivileged women, which increase the
20 still substantial burden of maternal morbidity and mortality. If we succeed in identifying
21 “specific patterns of physical activity and sleep” that are predictors of pregnancy
22 complications, further validation studies are recommended to assess the effectiveness
23 of screening procedures in management of these conditions. In addition, MAES-I will
24 permit further specific studies among a high-risk population and also help to identify the
25 best gestational age for monitoring, targeting a specific gestational age interval.

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1 Abbreviations

ANC – antenatal care	min – minutes
BMI – body mass index	mg – milligram
BP – blood pressure	mL – millilitre
CPM – count per minute	mmol – millimole
dL – decilitre	NICE – National Institute for Health and Care Excellence
FAQ – frequently asked questions	PA – physical activity
h – hour	PI – Principal investigator
HDI – human development index	SE – sleep efficiency
Hz - hertz	SCOPE – SCReening Of Pregnancy Endpoints
Kg – kilogram	SOL – sleep onset latency
L – litre	TST – total nocturnal sleep time
MAES-I – maternal Actigraphy Exploratory Study I	US – United States
MEMS – microelectromechanical	USA – United States of America
MET – metabolic equivalent	w – week
METs – metabolic equivalents	

Competing interests

The authors declare that they have no competing interests.

Author contributions

All authors contributed to the overall study design and specific methodologies. RTS, JGC, JM, MLC and JPS conceived the study design and wrote the first version of the study protocol. In a first meeting, the protocol was discussed and incorporated suggestions from RBG, FEF, ERF, DFL, JV, RPT and DSS. RTS, JGC, JM, and RBG planned the implementation of the study and developed the necessary material. RTS, JM, MLC and JGC drafted the manuscript that was afterwards revised by all other authors who gave suggestions. All authors discussed and made important contributions to the manuscript, read and approved the final version for submission.

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Table 1. Participating centres in the Maternal Actigraphy Exploratory Study I (MAES-I)

<ul style="list-style-type: none"> • The Maternity of CAISM, University of Campinas, in Campinas, SP, Brazil; <ul style="list-style-type: none"> ○ Local Principal Investigator: Maria Laura Costa.
<ul style="list-style-type: none"> • Maternity of the Clinic Hospital, Federal University of RS, Porto Alegre, RS, Brazil; <ul style="list-style-type: none"> ○ Local Principal Investigator: Janete Vettorazzi.
<ul style="list-style-type: none"> • Maternity of the University Hospital, Jundiaí Medical School in Jundiaí, SP, Brazil; <ul style="list-style-type: none"> ○ Local Principal Investigator: Ricardo Porto Tedesco.
<ul style="list-style-type: none"> • Maternity of Clinic Hospital, Federal University of Pernambuco, in Recife, PE, Brazil; <ul style="list-style-type: none"> ○ Local Principal Investigator: Edilberto A Rocha Filho.
<ul style="list-style-type: none"> • MEAC – School Maternity of the Federal University of Ceará, in Fortaleza, CE, Brazil. <ul style="list-style-type: none"> ○ Local Principal Investigator: Francisco Edson de Lucena Feitosa.

Table 2. Inclusion and Exclusion Criteria of MAES – I

Inclusion Criteria	
<ul style="list-style-type: none"> • Singleton pregnancy • Nulliparous (who had never given birth before) • Between 19+0 – 21+0 weeks of gestation 	
Exclusion Criteria	
<ul style="list-style-type: none"> • Unsure LMP and unwilling to date the Ultrasound • ≥ 3 Miscarriages • Major Fetal Anomaly/Abnormal Karyotype* • Essential Hypertension treated before pregnancy • Mod-Severe Hypertension at booking ($\geq 160/100$ mmHg) or Chronic hypertension using antihypertensive medication • Pre-pregnancy Diabetes • Renal Disease • Systemic Lupus Erythematosus • Anti-phospholipid Syndrome • Sickle Cell Disease • HIV or Hep B or Hep C positive • Any condition that limits the performance of physical activity 	<ul style="list-style-type: none"> • Major Uterine Anomaly • Cervical Suture • Knife cone biopsy • Ruptured membranes • Use of long-term steroids • Use of Low-dose Aspirin • Use of Calcium ($> 1g/24h$) • Use of Eicosapentaenoic acid (fish oil) $> 2,7g$ • Use of Vit. C $\geq 1000mg$ & Vit. E ≥ 400 UI • Use of Heparin/LMW Heparin • Untreated Thyroid disease • Use of antidepressant and/or anxiolytic agents

* All information on fetal anomalies will be properly recorded

Table 3. Measurement frequency and maximum return periods according to gestational age – MAES I

Gestational age	Measurement frequency	Maximum return period (weeks)
19 – 32 weeks	20Hz	4
33 – 36 weeks	30Hz	2
37 – 42 weeks	50Hz	1

Table 4. Performance of wrist and hip actigraphy methods according to different activities

	Hip			Wrist		
	Sens	Spec	BA	Sens	Spec	BA
Sitting	0.894	0.923	0.908	0.883	0.870	0.876
Vehicle	0.870	0.987	0.929	0.823	0.964	0.893
Walking/running	0.687	0.981	0.834	0.574	0.983	0.779
Standing	0.797	0.929	0.851	0.687	0.904	0.795
Average	0.812	0.955	0.881	0.742	0.930	0.836

BA: balanced accuracy; sens: sensitivity; spec: specificity

Adapted from Ellis K *et al.* Hip and Wrist Accelerometer Algorithms for Free-Living Behaviour Classification. *Med. Sci. Sports Exerc.* 2016.

Table 5. Severe Neonatal Morbidity definition according to term/preterm status

Preterm	Term
Grade III and IV intraventricular haemorrhage	Grade II or III hypoxic ischemic encephalopathy
Chronic lung disease (home O ₂ therapy or O ₂ therapy at 36 weeks gestation)	Ventilation>24 hours
Necrotizing enterocolitis	Neonatal intensive care admission >4 days
Retinopathy of prematurity, stage 3 or 4	Apgar score <4 at 5 mins
Sepsis (blood or CSF culture proven)	Cord arterial pH<7.0 and/or base excess>-15
Cystic peri-ventricular leukomalacia	Neonatal seizures

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3 **Figure legends:**
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6 **Figure 1.** Set points of MAES-I study
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8 **Figure 2.** Estimated prevalence of preterm birth and preeclampsia according to
9 gestational age (RED represents the majority of cases) and evaluation period of PA and
10 sleep patterns (in GREY)
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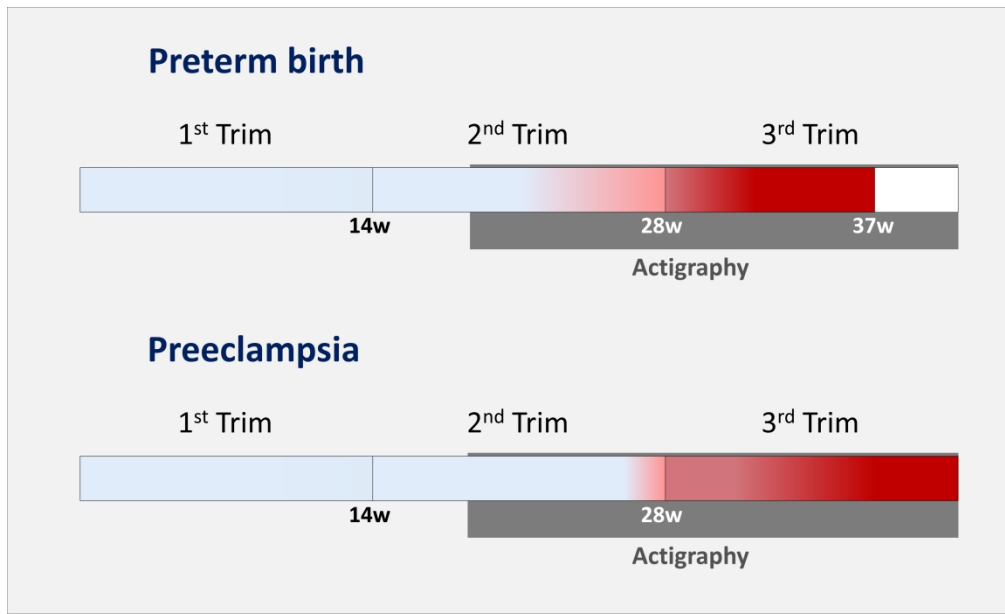


Figure 1

402x244mm (300 x 300 DPI)

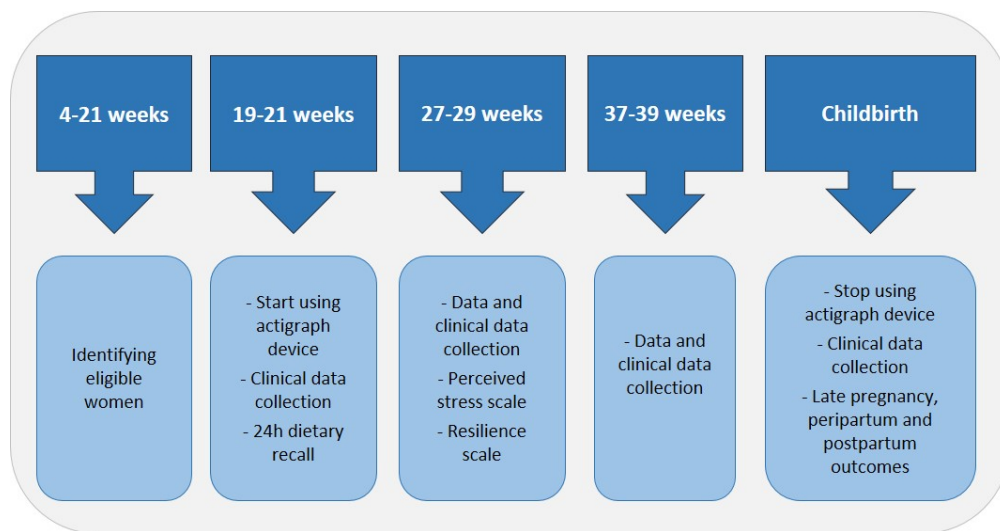


Figure 2

90x47mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1,2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	1,2,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	7,8
		(b) <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-15
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-15
Bias	9	Describe any efforts to address potential sources of bias	16,17
Study size	10	Explain how the study size was arrived at	15
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	16,17
		(b) Describe any methods used to examine subgroups and interactions	16,17
		(c) Explain how missing data were addressed	17
		(d) <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	n/a
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	n/a
			n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	7,8
			n/a
Outcome data	15*	<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	n/a
			n/a
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
			n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	17
Discussion			
Key results	18	Summarise key results with reference to study objectives	n/a
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.