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I-ACT: Integrated study on effect of Activity on ComplicaTions in pregnancy – study protocol of a multi-ethnic prospective cohort study

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I-ACT: Integrated study on effect of Activity on ComplicaTions in pregnancy – study protocol of a multi-ethnic prospective cohort study

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Abstract

Introduction: Physical activity (PA) during first 20 weeks of pregnancy may lower risks of gestational diabetes mellitus (GDM) and gestational hypertension (GH), though evidence of association remains inconclusive. Current studies rely heavily on subjective assessment of PA levels. Wearable activity trackers provide a convenient and objective surrogate index for PA validated by evidence-based steps/day categorization along a physical inactivity/activity continuum. I-ACT primarily aims to examine objectively measured PA levels and patterns in first and second trimesters of pregnancy and the association with GDM and/or GH in Singapore, a multi-ethnic Asian population. Secondary aims include investigating the bio-socio-demographic factors associated with sedentary behavior, and association of early pregnancy PA level with maternal weight at 6 weeks post-delivery. Results may facilitate identification of high-risk mothers-to-be and formulation of interventional strategies.

Methods and analysis: Prospective cohort study that will recruit 408 women at first antenatal visit at <12 weeks gestation. Baseline bio-socio-demographic factors and PA levels assessed by participant characteristics form and the International Physical Activity Questionnaire (IPAQ) respectively. An activity tracker (Fitbit) will be provided to be worn daily from date of recruitment to end of 20 weeks gestation. Tracker-recorded data will be synchronized with an application on participant's smartphone. Compliance will be reinforced with fortnightly reminders. After 20 weeks, a second IPAQ and a feedback form will be administered. GDM screened at 24-28 weeks gestation. GH diagnosed after 20 weeks gestation. Maternal weight assessed at 6 weeks post-delivery. Appropriate statistical tests will be used to compare continuous and categorical PA measurements between first and second trimesters. Logistic regression will be used to analyse associations.

Ethics and dissemination: Ethical approval obtained from the Centralised Institutional Review Board of SingHealth (reference 2017/2836). Dissemination of results will be via peer-reviewed research publications both online and in print, conference presentations, posters, and medical forums.

(299 words)

Keywords: Physical activity, gestational diabetes mellitus, pregnancy-induced hypertension, pregnancy

Article summary

Strengths and limitations of this study

- Prospective cohort study of a multi-ethnic Asian population
- Objective measurement of PA levels and patterns in early pregnancy
- Data collection designed to minimize recall bias
- Participant non-compliance despite reinforcement measures
- Participants' unfamiliarity with wearable activity tracker and mobile application despite education at recruitment

Introduction

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that results in energy expenditure[1]. Current recommendations encourage women with uncomplicated pregnancies to continue or initiate safe physical activities in pregnancy[2]. More specifically, the CDC recommends 30 min/day for five days each week of moderate-intensity aerobic activity, which can be met by walking[3]. Concerns about safety have been refuted by literature demonstrating that moderate exercise in low-risk pregnancy improves maternal well-being without associated risks of birth weight reduction or preterm birth[4].

Physical inactivity or sedentary behavior in early pregnancy (<20 weeks gestation) is a potential modifiable risk factor for two common obstetric complications, gestational diabetes mellitus (GDM) and gestational hypertension (GH). GDM is defined as carbohydrate intolerance that develops during pregnancy[5]. It complicates 1.8-25.1% of pregnancies worldwide depending on country and definition, with South-East Asia having the second highest prevalence at 8.1-18.3[6]. Approximately 8-20% of pregnancies are affected in Singapore[7]. Overall prevalence of GH, otherwise known as pregnancy-induced hypertension, is estimated at 10-12%[8,9], though the local incidence has not been established. Perinatal sequelae of GDM and GH include macrosomia, neonatal hypoglycemia, preterm birth, intrauterine growth restriction (IUGR), and low APGAR scores. Both metabolic disorders are also proven risk factors of future type 2 diabetes[10].

Current literature investigating the association between PA in early pregnancy and the development of GDM has shown a significant risk reduction of up to 24%[11-14], though a few other studies have found a null association[15,16]. The association with GH is even less clear from the limited literature available[17-20]. All these studies utilised questionnaires as a measurement of PA. Studies that incorporate an objective means of measurement have been scarce[21,22], which may partially explain the inconclusive evidence of association thus far. A Norway-based study investigating objectively recorded PA in early pregnancy and GDM reported that the adjusted odds ratio for GDM decreased 19% with every 3159 step-increase per day[21]. Based on these existing studies, physical inactivity in early pregnancy is a modifiable risk factor worth targeting

This is especially so in the Asian population. PA during first half of pregnancy has been shown to be low in an Asian urban setting[23], and similarly lower when compared to non-Asian counterparts[22,24]. In Singapore, no published study on objectively measured PA levels in pregnancy could be found, and studies on association of subjectively-measured early pregnancy PA levels with both obstetric complications are rare. Padmapriya *et al.* investigated the change in PA levels from a pre-pregnancy to pregnancy state using a structured self-constructed questionnaire administered at 26-28 weeks gestation scored based on the International Physical Activity Questionnaire (IPAQ) short form[25]. The same study group further reported that a higher PA during the first 6 months of pregnancy was associated with lower prevalence of GDM, especially among overweight/obese women[26]. However, the utilisation of a questionnaire at 26-28 weeks gestation that relied on recall of PA levels during first 6 months of pregnancy and the year before subjected the results to a high level of recall bias. Therefore, the paucity of local research on objectively-measured PA levels in early pregnancy and association with obstetric metabolic outcomes warrants additional prospective studies.

As evident from existing studies, current assessment of pregnancy PA levels relies heavily on subjective, self-reporting questionnaires deemed to be the most feasible method with the absence of a gold standard and clear guidelines[27]. The inclusion of more objective measurements is being advocated[28]. Consumer wearable activity trackers operate through a 3-axis accelerometer, providing an alternative convenient and objective means of assessing PA levels during pregnancy. The accuracy, reliability and efficacy of wearable activity trackers in various health programs have been validated[29-32]. Steps per day categorization along a physical inactivity/activity continuum based on CDC recommendation has also been elucidated, with 5000 (sedentary) and 10,000 (active) being the primary anchor points[33]. The correlation between steps per day and activity counts per day, from which activity intensity and duration were derived, was proven to be positive and strong, thus validating its use as an index for PA[34]. Step count estimated by Fitbit activity trackers in particular has also been validated in a separate study[35].

Through the use of both Fitbit activity trackers and the IPAQ, this prospective multi-ethnic cohort study primarily aims to investigate the PA levels and patterns in early pregnancy (1st trimester and 2nd trimester up to 20 weeks gestation), as well as the effect of PA in early pregnancy on development of GDM and/or GH. Secondary aims include assessing the bio-socio-demographic factors associated with sedentary behavior, and examining the association between early pregnancy PA level and maternal weight at 6 weeks post-delivery.

Methods and analysis

Study design

In this prospective cohort study, pregnant women will be recruited at outpatient clinics in KK Women's and Children's Hospital, a major public hospital in Singapore that sees a high volume of obstetrics & gynaecology consultations.

Recruitment and eligibility criteria

All obstetricians running outpatient general obstetrics & gynaecology clinics will refer suitable candidates for recruitment. All recruitment will be done via face-to-face contact by the research team.

Inclusion criteria are singleton pregnancy, first antenatal visit less than 12 weeks gestation, and ages between 21 and 50 years old inclusive. Exclusion criteria are severe medical and/or psychological co-morbidity (including New York Heart Association (NYHA) class IV heart failure, end-stage renal disease, assistive device-dependent for mobility, cognitive impairment, and loss of rational thinking), and skin conditions (including contact dermatitis, pemphigus vulgaris and bullous pemphigoid) precluding the wearing of activity trackers.

Power analysis

Given that prevalence of GH has not been investigated in Singapore, GDM prevalence is used instead. Assuming that GDM proportion is 17.6%[36] and that PA can reduce risk of GDM by 30%, a sample of 367 mothers will be required at 80% power and 5% level of significance. Assuming a dropout rate of 10%, a sample of 408 mothers will be recruited into the study.

Participant timeline

Recruitment is at first antenatal visit less than 12 weeks gestation, during which Fitbit education, International Physical Activity Questionnaire (IPAQ) and participant characteristics form are done (Fig. 1). PA level monitoring occurs henceforth until end of 20 weeks gestation inclusive. The standard 4-weekly antenatal visits will continue during this period. After 20 weeks gestation, a second IPAQ and a feedback form are administered either at regular antenatal visits before 24 weeks gestation, or over the phone/email. Routine GDM screening takes place between 24 and 28 weeks gestation. The final follow-up occurs at the 6th week after delivery to obtain participants' weight.

Ensuring compliance

Approaches to enhance compliance include reinforcing the importance of commitment to wearing the activity trackers daily at the time of recruitment, and making fortnightly follow-

up calls up until 20 weeks gestation. Compliance will also be recorded as part of Fitbit use assessment in the participant feedback form at the end of 20 weeks gestation.

Outcome measures

Primary outcomes include the following:

- GDM – diagnosed if the following threshold value at any time point is exceeded after a 75 g oral glucose tolerance test (OGTT) between 24 and 28 weeks gestation based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria: fasting venous plasma glucose of ≥5.1 mmol/L, 1-hour venous plasma glucose of ≥10.0 mmol/L, and 2-hour venous plasma glucose ≥8.5 mmol/L[37].
- GH – diagnosed as new onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) measured on two occasions at least four hours apart after 20 weeks gestation in the absence of proteinuria or new signs of end-organ dysfunction[38].

Secondary outcomes include the following:

- Weight at 6 weeks post-delivery
- Weight gain in pregnancy
- Intrauterine growth restriction (IUGR)
- Preterm birth (GA <37 weeks)
- Macrosomia (BW >4.5kg)
- Neonatal hypoglycemia (glucose <2.5 mmol/L)
- Pre-eclampsia
- APGAR scores

Data collection

Research participant characteristics form

Sociodemographic data to be assessed include marital status, educational level, household income, type of housing, working status during pregnancy, smoking status, and alcohol consumption. Medical history including pre-pregnancy height and weight, parity, history of infertility treatment, existing chronic illnesses, history of GDM and/or GH, family history of DM, and reasons behind potential PA restriction during early pregnancy will also be collected.

Fitbit activity tracker and mobile application

At recruitment, each participant is given a wristband activity tracker (Fitbit) that will be connected via Bluetooth to a Fitbit application downloaded onto her smartphone. Education on device and application will be carried out. The tracker is worn daily from recruitment to end of 20 weeks gestation inclusive, except during bathing or water activities. Participants are advised to synchronize the tracker data at least once a week. For data to be valid, wear-time must be at least 4 days per week (including one weekend day) and at least 10 hours per day.

Steps per day will be recorded by the tracker. Data will be reported as continuous and categorical variables. Continuous variables include mean weekday and weekend steps per day and mean steps per day in first and second trimesters. Categorical variables include classification into a CDC recommendation-based steps per day physical inactivity/activity continuum defined as follows: (1) <5000 (sedentary); (2) 5000-7499 (low active); 3) 7500-9999 (somewhat active); 4) 10,000-12,499 (active); and 5) ≥12,500 (highly active)[33].

International Physical Activity Questionnaire (IPAQ)

The IPAQ long version will be self-administered during the first visit at less than 12 weeks gestation in the first trimester and again between 20-24 weeks gestation in the second trimester. It is a set of 4 questionnaires assessing 5 activity domains (occupation, transportation, household, leisure, and sedentary) independently in the past 7 days, and may be administered via self or telephone[39]. Well-established and validated in adults aged 15-69 years, it is available in both English and Chinese[40,41]. It has been used in studies involving pregnant women[28,42].

Data will be reported as continuous and categorical variables. Continuous variables include median MET-minutes per week (MET-min/wk) and interquartile ranges computed for each domain, subdomain (walking, moderate-intensity PA and vigorous-intensity PA) and overall total PA. MET or metabolic equivalent is a unit that measures energy expenditure in multiples of the resting metabolic rate[43]. Categorical variables include classification into low, moderate, high levels of PA according to the IPAQ scoring protocol.

Medical record data

Additional data to be collected include ethnicity, weight changes during pregnancy, weight at 6 weeks post-delivery, obstetric outcomes of GDM, GH, preeclampsia and IUGR, and neonatal outcomes comprising APGAR scores, preterm birth, macrosomia, and neonatal hypoglycemia.

Participant feedback form

After the end of 20 weeks gestation, experience with the activity tracker and mobile application in terms of usability and troubleshooting will be evaluated. Compliance level will be quantified by number of days per week.

Statistics

Descriptive statistics of PA levels in the 1st and early 2nd trimester will be presented. Mean steps per day and median MET-minutes per week between semesters will be compared using paired Student's t-test and Wilcoxon signed-rank test respectively. McNemar's test will be used to compare sedentary behavior between semesters. Similar tests will be used to assess for a difference in PA levels between weekdays and weekends.

Logistic regression will be used to evaluate bio-socio-demographic factors associated with sedentary behavior, and the effect of early pregnancy PA on GDM and/or GH.

Statistical analyses will be performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, N.Y., USA). *P* values of <0.05 will be considered statistically significant.

Safety parameters

Adverse effects and device monitoring will be carried out at the subsequent 4-weekly routine prenatal visits. Any adverse skin reaction to the wristband will be recorded. Participation will be stopped at any time the Principal Investigator decides that continuing on could be harmful to the participant.

Data management

All data will be coded for confidentiality. Hardcopy data will be stored at the research site under lock and key. Electronic data can only be accessed and retrieved from the secured website by the participant and research team. All data obtained will be entered into and stored on the institution Research Electronic Data Capture (REDCap) system, a centralised secured data management server with password access. Data integrity monitoring will be carried out monthly by the principal investigator and co-investigators if deemed necessary.

Ethics and dissemination

Ethical approval was obtained from the Centralised Institutional Review Board of SingHealth (reference 2017/2836). Informed written consent will be sought from all participants.

Results from this study will be submitted to the funding organization and peer-reviewed journals for consideration of publication both online and in print. Results will also be presented at relevant meetings, conferences and medical forums in either oral or poster formats.

Conclusion

The I-ACT study aims to be the first comprehensive study objectively evaluating the PA levels and patterns in early pregnancy, and their association with GDM and/or GH in the multi-ethnic population of Singapore. In addition to addressing these important scientific knowledge gaps, from a clinical perspective, the study itself may increase awareness of PA during early pregnancy while demonstrating the potential of wearable activity trackers as an objective measure of PA in health research. More importantly, we hope the results of the study facilitate the identification of high-risk mothers-to-be for targeted intervention, and help formulate strategies for interventional efforts.

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Author statement

MC was involved in all aspects of the study from conception, design, recruitment and manuscript writing. KHT and SBA provided critical review of the design and writing. As

Principle Investigator, SBA takes overall responsibility for the work. All authors agree to be accountable for their work.

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Conflict of interests

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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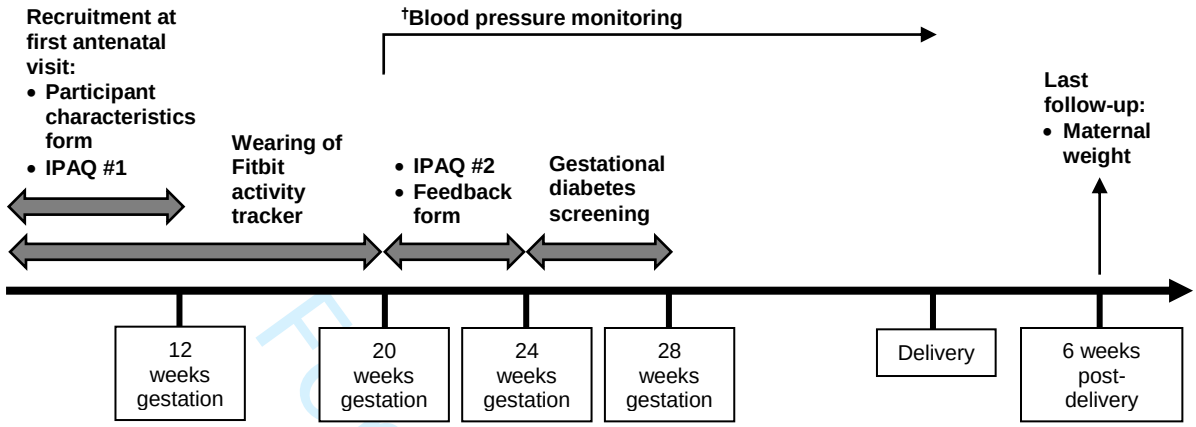

†Participants will continue to attend routine antenatal visits throughout the study period during which blood pressure monitoring will be done

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Introduction

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that results in energy expenditure[1]. Current recommendations encourage women with uncomplicated pregnancies to continue or initiate safe physical activities in pregnancy[2]. More specifically, the CDC recommends 30 min/day for five days each week of moderate-intensity aerobic activity, which can be met by walking[3]. Concerns about safety have been refuted by literature demonstrating that moderate exercise in low-risk pregnancy improves maternal well-being without associated risks of birth weight reduction or preterm birth[4].

Physical inactivity or sedentary behavior in early pregnancy (<20 weeks gestation) is a potential modifiable risk factor for two common obstetric complications, gestational diabetes mellitus (GDM) and gestational hypertension (GH). GDM is defined as carbohydrate intolerance that develops during pregnancy[5]. It complicates 1.8-25.1% of pregnancies worldwide depending on country and definition, with South-East Asia having the second highest prevalence at 8.1-18.3[6]. Approximately 8-20% of pregnancies are affected in Singapore[7]. Overall prevalence of GH, otherwise known as pregnancy-induced hypertension, is estimated at 10-12%[8,9], though the local incidence has not been established. Perinatal sequelae of GDM and GH include macrosomia, neonatal hypoglycemia, preterm birth, intrauterine growth restriction (IUGR), and low APGAR scores. Both metabolic disorders are also proven risk factors of future type 2 diabetes[10].

Current literature investigating the association between PA in early pregnancy and the development of GDM has shown a significant risk reduction of up to 24%[11-14], though a few other studies have found a null association or insufficient evidence[15-17]. The association with GH is even less clear from the limited literature available[18-21]. All these studies utilised questionnaires as a measurement of PA. Studies that incorporate an objective means of measurement have been scarce[22,23], which may partially explain the inconclusive evidence of association thus far. A Norway-based study investigating objectively recorded PA in early pregnancy and GDM reported that the adjusted odds ratio for GDM decreased 19% with every 3159 step-increase per day[22]. Based on these existing studies, physical inactivity in early pregnancy is a modifiable risk factor worth targeting

This is especially so in the Asian population. PA during first half of pregnancy has been shown to be low in an Asian urban setting[24], and similarly lower when compared to non-Asian counterparts[23,25]. In Singapore, no published study on objectively measured PA levels in pregnancy could be found, and studies on association of subjectively-measured early pregnancy PA levels with both obstetric complications are rare. Padmapriya *et al*. investigated the change in PA levels from a pre-pregnancy to pregnancy state using a structured self-constructed questionnaire administered at 26-28 weeks gestation scored based on the International Physical Activity Questionnaire (IPAQ) short form[26]. The same study group further reported that a higher PA during the first 6 months of pregnancy was associated with lower prevalence of GDM, especially among overweight/obese women[27]. However, the utilisation of a questionnaire at 26-28 weeks gestation that relied on recall of PA levels during first 6 months of pregnancy and the year before subjected the results to a high level of recall bias. Therefore, the paucity of local research on objectively-measured PA levels in early pregnancy and association with obstetric metabolic outcomes warrants additional prospective studies.

As evident from existing studies, current assessment of pregnancy PA levels relies heavily on subjective, self-reporting questionnaires deemed to be the most feasible method with the absence of a gold standard and clear guidelines[28]. The inclusion of more objective measurements is being advocated[29]. Consumer wearable activity trackers operate through a 3-axis accelerometer, providing an alternative convenient and objective means of assessing PA levels during pregnancy. The accuracy, reliability and efficacy of wearable activity trackers in various health programs have been validated[30-33], although a systematic review has found the research-grade accelerometer or pedometer to be superior in terms of accuracy[34]. Steps per day categorization along a physical inactivity/activity continuum based on CDC recommendation has also been elucidated, with 5000 (sedentary) and 10,000 (active) being the primary anchor points[35]. The correlation between steps per day and activity counts per day, from which activity intensity and duration were derived, was proven to be positive and strong, thus validating its use as an index for PA[36]. Step count estimated by Fitbit activity trackers among healthy adults has also been validated in a separate study[37]. Furthermore, various measured parameters such as step count and moderate-to-vigorous PA (MVPA) of different Fitbit activity trackers models have also been validated in the particular population of pregnant women in free living conditions[38].

Through the use of both Fitbit activity trackers and the IPAQ, this prospective multi-ethnic cohort study primarily aims to investigate the PA levels and patterns in early pregnancy (1st trimester and 2nd trimester up to 20 weeks gestation), as well as the effect of PA in early pregnancy on development of GDM and/or GH. Secondary aims include assessing the bio-socio-demographic factors associated with sedentary behavior, and examining the association between early pregnancy PA level and maternal weight at 6 weeks post-delivery.

Methods and analysis

Study design

In this prospective cohort study, pregnant women will be recruited at outpatient clinics in KK Women's and Children's Hospital, a major public hospital in Singapore that sees a high volume of obstetrics & gynaecology consultations. Recruitment started in June 2018 and is expected to end in 2019. This study will follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Recruitment and eligibility criteria

All obstetricians running outpatient general obstetrics & gynaecology clinics will refer suitable candidates for recruitment. All recruitment will be done via face-to-face contact by the research team.

Inclusion criteria are singleton pregnancy, first antenatal visit less than 12 weeks gestation, and ages between 21 and 50 years old inclusive. Exclusion criteria are severe medical and/or psychological co-morbidity (including New York Heart Association (NYHA) class IV heart failure, end-stage renal disease, assistive device-dependent for mobility, cognitive impairment, and loss of rational thinking), and skin conditions (including contact dermatitis, pemphigus vulgaris and bullous pemphigoid) precluding the wearing of activity trackers.

Power analysis

Given that prevalence of GH has not been investigated in Singapore, GDM prevalence is used instead. Assuming that GDM proportion is 17.6%[39] and that PA can reduce risk of GDM by 30%, a sample of 367 mothers will be required at 80% power and 5% level of significance. Assuming a dropout rate of 10%, a sample of 408 mothers will be recruited into the study.

Participant timeline

Recruitment is at first antenatal visit less than 12 weeks gestation, during which Fitbit education, International Physical Activity Questionnaire (IPAQ) and participant characteristics form are done (Fig. 1). PA level monitoring occurs henceforth until end of 20 weeks gestation inclusive. The standard 4-weekly antenatal visits will continue during this period. After 20 weeks gestation, a second IPAQ and a feedback form are administered either at regular antenatal visits before 24 weeks gestation, or over the phone/email. Routine GDM screening takes place between 24 and 28 weeks gestation. The final follow-up occurs at the 6th week after delivery to obtain participants' weight.

Ensuring compliance

Approaches to enhance compliance include reinforcing the importance of commitment to wearing the activity trackers daily at the time of recruitment, and making fortnightly follow-up calls up until 20 weeks gestation. Compliance will also be recorded as part of Fitbit use assessment in the participant feedback form at the end of 20 weeks gestation.

Outcome measures

Primary outcomes include the following:

- GDM – diagnosed if the following threshold value at any time point is exceeded after a 75 g oral glucose tolerance test (OGTT) between 24 and 28 weeks gestation based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria: fasting venous plasma glucose of ≥5.1 mmol/L, 1-hour venous plasma glucose of ≥10.0 mmol/L, and 2-hour venous plasma glucose ≥8.5 mmol/L[40].
- GH – diagnosed as new onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) measured on two occasions at least four hours apart after 20 weeks gestation in the absence of proteinuria or new signs of end-organ dysfunction[41].

Secondary outcomes include the following:

- Weight at 6 weeks post-delivery
- Weight gain in pregnancy
- Intrauterine growth restriction (IUGR)
- Preterm birth (GA <37 weeks)
- Macrosomia (BW >4.5kg)
- Neonatal hypoglycemia (glucose <2.5 mmol/L)
- Pre-eclampsia
- APGAR scores

Data collection

Research participant characteristics form

Sociodemographic data to be assessed include marital status, educational level, household income, type of housing, working status during pregnancy, smoking status, and alcohol consumption. Medical history including pre-pregnancy height and weight, parity, history of infertility treatment, existing chronic illnesses, history of GDM and/or GH, family history of DM, and reasons behind potential PA restriction during early pregnancy will also be collected.

Fitbit activity tracker and mobile application

At recruitment, each participant is given a wristband activity tracker (Fitbit) that will be connected via Bluetooth to a Fitbit application downloaded onto her smartphone. Education on device and application will be carried out. The tracker is worn daily from recruitment to

end of 20 weeks gestation inclusive, except during bathing or water activities. Participants are advised to synchronize the tracker data at least once a week. For data to be valid, wear-time must be at least 4 days per week (including one weekend day) and at least 10 hours per day.

Steps per day will be recorded by the tracker. Data will be reported as continuous and categorical variables. Continuous variables include mean weekday and weekend steps per day and mean steps per day in first and second trimesters. Categorical variables include classification into a CDC recommendation-based steps per day physical inactivity/activity continuum defined as follows: (1) <5000 (sedentary); (2) 5000-7499 (low active); 3) 7500-9999 (somewhat active); 4) 10,000-12,499 (active); and 5) ≥12,500 (highly active)[35].

International Physical Activity Questionnaire (IPAQ)

The IPAQ long version will be self-administered during the first visit at less than 12 weeks gestation in the first trimester and again between 20-24 weeks gestation in the second trimester. It is a set of 4 questionnaires assessing 5 activity domains (occupation, transportation, household, leisure, and sedentary) independently in the past 7 days, and may be administered via self or telephone[42]. Well-established and validated in adults aged 15-69 years, it is available in both English and Chinese[43,44]. It has been used in studies involving pregnant women[29,45].

Data will be reported as continuous and categorical variables. Continuous variables include median MET-minutes per week (MET-min/wk) and interquartile ranges computed for each domain, subdomain (walking, moderate-intensity PA and vigorous-intensity PA) and overall total PA. MET or metabolic equivalent is a unit that measures energy expenditure in multiples of the resting metabolic rate[46]. Categorical variables include classification into low, moderate, high levels of PA according to the IPAQ scoring protocol.

Medical record data

Additional data to be collected include ethnicity, weight changes during pregnancy, weight at 6 weeks post-delivery, obstetric outcomes of GDM, GH, preeclampsia and IUGR, and neonatal outcomes comprising APGAR scores, preterm birth, macrosomia, and neonatal hypoglycemia.

Participant feedback form

After the end of 20 weeks gestation, experience with the activity tracker and mobile application in terms of usability and troubleshooting will be evaluated. Compliance level will be quantified by number of days per week.

Statistics

Descriptive statistics of PA levels in the 1st and early 2nd trimester will be presented. Categorical variables will be presented as n (%) while continuous variables will be presented

as mean (SD) or median (SD). Mean steps per day and median MET-minutes per week between semesters will be compared using paired Student's t-test and Wilcoxon signed-rank test respectively. McNemar's test will be used to compare sedentary behavior between semesters. Similar tests will be employed to assess for a difference in PA levels between weekdays and weekends.

Binary logistic regression will be used to evaluate the association of early pregnancy PA with GDM and/or GH. Crude (unadjusted) and adjusted regression models will be included. Potential confounders will be identified a priori based on literature review and controlled for in the regression analyses. Potential interactions between covariates and early pregnancy PA will be tested using cross-product terms. Secondary analyses on the bio-socio-demographic factors associated with sedentary behavior, as well as the association between early pregnancy PA level and maternal weight at 6 weeks post-delivery, will follow the methods of the primary analyses, but are exploratory having not been powered to formally test the hypotheses. All regression analyses will be presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Statistical analyses will be performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, N.Y., USA). *P* values of <0.05 will be considered statistically significant.

Safety parameters

Adverse effects and device monitoring will be carried out at the subsequent 4-weekly routine prenatal visits. Any adverse skin reaction to the wristband will be recorded. Participation will be stopped at any time the Principal Investigator decides that continuing on could be harmful to the participant.

Data management

All data will be coded for confidentiality. Hardcopy data will be stored at the research site under lock and key. Electronic data can only be accessed and retrieved from the secured website by the participant and research team. Electronic data will be exported on a fortnightly basis. All data obtained will be entered into and stored on the institution Research Electronic Data Capture (REDCap) system, a centralised secured data management server with password access. Data integrity monitoring will be carried out monthly by the principal investigator and co-investigators if deemed necessary.

Patient and Public Involvement

Patients and the public were not involved in the development of the research question and outcome measures.

Ethics and dissemination

Ethical approval was obtained from the Centralised Institutional Review Board of SingHealth (reference 2017/2836). Informed written consent will be sought from all participants.

Results from this study will be submitted to the funding organization and peer-reviewed journals for consideration of publication both online and in print. Results will also be presented at relevant meetings, conferences and medical forums in either oral or poster formats.

Conclusion

The I-ACT study aims to be the first comprehensive study objectively evaluating the PA levels and patterns in early pregnancy, and their association with GDM and/or GH in the multi-ethnic population of Singapore. In addition to addressing these important scientific knowledge gaps, from a clinical perspective, the study itself may increase awareness of PA during early pregnancy while demonstrating the potential of wearable activity trackers as an objective measure of PA in health research. More importantly, we hope the results of the study facilitate the identification of high-risk mothers-to-be for targeted intervention, and help formulate strategies for interventional efforts.

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Author statement

MC was involved in all aspects of the study from conception, design, recruitment and manuscript writing. KHT and SBA provided critical review of the design and writing. As Principle Investigator, SBA takes overall responsibility for the work. All authors agree to be accountable for their work.

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Conflict of interests

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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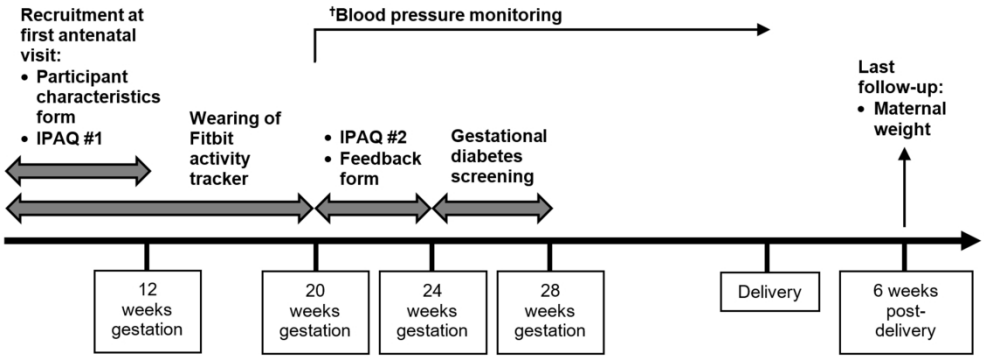
Figure Legend

Figure 1. Timeline of the I-ACT prospective cohort study.
†Participants will continue to attend routine antenatal visits throughout the study period during which blood pressure monitoring will be done.



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BMJ Open

I-ACT: Integrated study on effect of Activity on ComplicaTions in pregnancy – study protocol of a multi-ethnic prospective cohort study

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I-ACT: Integrated study on effect of Activity on ComplicaTions in pregnancy – study protocol of a multi-ethnic prospective cohort study

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Abstract

Introduction: Physical activity (PA) during first 20 weeks of pregnancy may lower risks of gestational diabetes mellitus (GDM) and gestational hypertension (GH), though evidence of association remains inconclusive. Current studies rely heavily on subjective assessment of PA levels. Wearable activity trackers provide a convenient and objective surrogate index for PA validated by evidence-based steps/day categorization along a physical inactivity/activity continuum. I-ACT primarily aims to examine objectively measured PA levels and patterns in first and second trimesters of pregnancy and the association with GDM and/or GH in Singapore, a multi-ethnic Asian population. Secondary aims include investigating the bio-socio-demographic factors associated with sedentary behavior, and association of early pregnancy PA level with maternal weight at 6 weeks post-delivery. Results may facilitate identification of high-risk mothers-to-be and formulation of interventional strategies.

Methods and analysis: Prospective cohort study that will recruit 408 women at first antenatal visit at <12 weeks gestation. Baseline bio-socio-demographic factors and PA levels assessed by participant characteristics form and the International Physical Activity Questionnaire (IPAQ) respectively. An activity tracker (Fitbit) will be provided to be worn daily from date of recruitment to end of 20 weeks gestation. Tracker-recorded data will be synchronized with an application on participant's smartphone. Compliance will be reinforced with fortnightly reminders. After 20 weeks, a second IPAQ and a feedback form will be administered. GDM screened at 24-28 weeks gestation. GH diagnosed after 20 weeks gestation. Maternal weight assessed at 6 weeks post-delivery. Appropriate statistical tests will be used to compare continuous and categorical PA measurements between first and second trimesters. Logistic regression will be used to analyse associations.

Ethics and dissemination: Ethical approval obtained from the Centralised Institutional Review Board of SingHealth (reference 2017/2836). Dissemination of results will be via peer-reviewed research publications both online and in print, conference presentations, posters, and medical forums.

(299 words)

Keywords: Physical activity, gestational diabetes mellitus, pregnancy-induced hypertension, pregnancy

Article summary

Strengths and limitations of this study

- Prospective cohort study of a multi-ethnic Asian population
- Objective measurement of PA levels and patterns in early pregnancy
- Data collection designed to minimize recall bias
- Participant non-compliance despite reinforcement measures
- Participants' unfamiliarity with wearable activity tracker and mobile application despite education at recruitment

Introduction

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that results in energy expenditure[1]. Current recommendations encourage women with uncomplicated pregnancies to continue or initiate safe physical activities in pregnancy[2]. More specifically, the CDC recommends 30 min/day for five days each week of moderate-intensity aerobic activity, which can be met by walking[3]. Concerns about safety have been refuted by literature demonstrating that moderate exercise in low-risk pregnancy improves maternal well-being without associated risks of birth weight reduction or preterm birth[4].

Physical inactivity or sedentary behavior in early pregnancy (<20 weeks gestation) is a potential modifiable risk factor for two common obstetric complications, gestational diabetes mellitus (GDM) and gestational hypertension (GH). GDM is defined as carbohydrate intolerance that develops during pregnancy[5]. It complicates 1.8-25.1% of pregnancies worldwide depending on country and definition, with South-East Asia having the second highest prevalence at 8.1-18.3[6]. Approximately 8-20% of pregnancies are affected in Singapore[7]. Overall prevalence of GH, otherwise known as pregnancy-induced hypertension, is estimated at 10-12%[8,9], though the local incidence has not been established. Perinatal sequelae of GDM and GH include macrosomia, neonatal hypoglycemia, preterm birth, intrauterine growth restriction (IUGR), and low APGAR scores. Both metabolic disorders are also proven risk factors of future type 2 diabetes[10].

Current literature investigating the association between PA in early pregnancy and the development of GDM has shown a significant risk reduction of up to 24%[11-14], though a few other studies have found a null association or insufficient evidence[15-17]. The association with GH is even less clear from the limited literature available[18-21]. All these studies utilised questionnaires as a measurement of PA. Studies that incorporate an objective means of measurement have been scarce[22,23], which may partially explain the inconclusive evidence of association thus far. A Norway-based study investigating objectively recorded PA in early pregnancy and GDM reported that the adjusted odds ratio for GDM decreased 19% with every 3159 step-increase per day[22]. Based on these existing studies, physical inactivity in early pregnancy is a modifiable risk factor worth targeting

This is especially so in the Asian population. PA during first half of pregnancy has been shown to be low in an Asian urban setting[24], and similarly lower when compared to non-Asian counterparts[23,25]. In Singapore, no published study on objectively measured PA levels in pregnancy could be found, and studies on association of subjectively-measured early pregnancy PA levels with both obstetric complications are rare. Padmapriya *et al*. investigated the change in PA levels from a pre-pregnancy to pregnancy state using a structured self-constructed questionnaire administered at 26-28 weeks gestation scored based on the International Physical Activity Questionnaire (IPAQ) short form[26]. The same study group further reported that a higher PA during the first 6 months of pregnancy was associated with lower prevalence of GDM, especially among overweight/obese women[27]. However, the utilisation of a questionnaire at 26-28 weeks gestation that relied on recall of PA levels during first 6 months of pregnancy and the year before subjected the results to a high level of recall bias. Therefore, the paucity of local research on objectively-measured PA levels in early pregnancy and association with obstetric metabolic outcomes warrants additional prospective studies.

As evident from existing studies, current assessment of pregnancy PA levels relies heavily on subjective, self-reporting questionnaires deemed to be the most feasible method with the absence of a gold standard and clear guidelines[28]. The inclusion of more objective measurements is being advocated[29]. Consumer wearable activity trackers operate through a 3-axis accelerometer, providing an alternative convenient and objective means of assessing PA levels during pregnancy. The accuracy, reliability and efficacy of wearable activity trackers in various health programs have been validated[30-33], although a systematic review has found the research-grade accelerometer or pedometer to be superior in terms of accuracy[34]. Steps per day categorization along a physical inactivity/activity continuum based on CDC recommendation has also been elucidated, with 5000 (sedentary) and 10,000 (active) being the primary anchor points[35]. The correlation between steps per day and activity counts per day, from which activity intensity and duration were derived, was proven to be positive and strong, thus validating its use as an index for PA[36]. Step count estimated by Fitbit activity trackers among healthy adults has also been validated in a separate study[37]. Furthermore, various measured parameters such as step count and moderate-to-vigorous PA (MVPA) of different Fitbit activity trackers models have also been validated in the particular population of pregnant women in free living conditions[38].

Through the use of both Fitbit activity trackers and the IPAQ, this prospective multi-ethnic cohort study primarily aims to investigate the PA levels and patterns in early pregnancy (1st trimester and 2nd trimester up to 20 weeks gestation), as well as the effect of PA in early pregnancy on development of GDM and/or GH. Secondary aims include assessing the bio-socio-demographic factors associated with sedentary behavior, and examining the association between early pregnancy PA level and maternal weight at 6 weeks post-delivery.

Methods and analysis

Study design

In this prospective cohort study, pregnant women will be recruited at outpatient clinics in KK Women's and Children's Hospital, a major public hospital in Singapore that sees a high volume of obstetrics & gynaecology consultations. Recruitment started in June 2018 and is expected to end in 2019. This study will follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Recruitment and eligibility criteria

All obstetricians running outpatient general obstetrics & gynaecology clinics will refer suitable candidates for recruitment. All recruitment will be done via face-to-face contact by the research team.

Inclusion criteria are singleton pregnancy, first antenatal visit less than 12 weeks gestation, and ages between 21 and 50 years old inclusive. Exclusion criteria are severe medical and/or psychological co-morbidity (including New York Heart Association (NYHA) class IV heart failure, end-stage renal disease, assistive device-dependent for mobility, cognitive impairment, and loss of rational thinking), and skin conditions (including contact dermatitis, pemphigus vulgaris and bullous pemphigoid) precluding the wearing of activity trackers.

Power analysis

Given that prevalence of GH has not been investigated in Singapore, GDM prevalence is used instead. Assuming that GDM proportion is 17.6%[39] and that PA can reduce risk of GDM by 30%, a sample of 367 mothers will be required at 80% power and 5% level of significance. Assuming a dropout rate of 10%, a sample of 408 mothers will be recruited into the study.

Participant timeline

Recruitment is at first antenatal visit less than 12 weeks gestation, during which Fitbit education, International Physical Activity Questionnaire (IPAQ) and participant characteristics form are done (Fig. 1). PA level monitoring occurs henceforth until end of 20 weeks gestation inclusive. The standard 4-weekly antenatal visits will continue during this period. After 20 weeks gestation, a second IPAQ and a feedback form are administered either at regular antenatal visits before 24 weeks gestation, or over the phone/email. Routine GDM screening takes place between 24 and 28 weeks gestation. The final follow-up occurs at the 6th week after delivery to obtain participants' weight.

Ensuring compliance

Approaches to enhance compliance include reinforcing the importance of commitment to wearing the activity trackers daily at the time of recruitment, and making fortnightly follow-up calls up until 20 weeks gestation. Compliance will also be recorded as part of Fitbit use assessment in the participant feedback form at the end of 20 weeks gestation.

Outcome measures

Primary outcomes include the following:

- GDM – diagnosed if the following threshold value at any time point is exceeded after a 75 g oral glucose tolerance test (OGTT) between 24 and 28 weeks gestation based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria: fasting venous plasma glucose of ≥5.1 mmol/L, 1-hour venous plasma glucose of ≥10.0 mmol/L, and 2-hour venous plasma glucose ≥8.5 mmol/L[40].
- GH – diagnosed as new onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) measured on two occasions at least four hours apart after 20 weeks gestation in the absence of proteinuria or new signs of end-organ dysfunction[41].

Secondary outcomes include the following:

- Weight at 6 weeks post-delivery
- Weight gain in pregnancy
- Intrauterine growth restriction (IUGR)
- Preterm birth (GA <37 weeks)
- Macrosomia (BW >90th percentile or >4.0 kg)
- Neonatal hypoglycemia (glucose <2.5 mmol/L)
- Pre-eclampsia
- APGAR scores

Data collection

Research participant characteristics form

Sociodemographic data to be assessed include marital status, educational level, household income, type of housing, working status during pregnancy, smoking status, and alcohol consumption. Medical history including pre-pregnancy height and weight, parity, history of infertility treatment, existing chronic illnesses, history of GDM and/or GH, family history of DM, and reasons behind potential PA restriction during early pregnancy will also be collected.

Fitbit activity tracker and mobile application

At recruitment, each participant is given a wristband activity tracker (Fitbit) that will be connected via Bluetooth to a Fitbit application downloaded onto her smartphone. Education on device and application will be carried out. The tracker is worn daily from recruitment to

end of 20 weeks gestation inclusive, except during bathing or water activities. Participants are advised to synchronize the tracker data at least once a week. For data to be valid, wear-time must be at least 4 days per week (including one weekend day) and at least 10 hours per day.

Steps per day will be recorded by the tracker. Data will be reported as continuous and categorical variables. Continuous variables include mean weekday and weekend steps per day and mean steps per day in first and second trimesters. Categorical variables include classification into a CDC recommendation-based steps per day physical inactivity/activity continuum defined as follows: (1) <5000 (sedentary); (2) 5000-7499 (low active); 3) 7500-9999 (somewhat active); 4) 10,000-12,499 (active); and 5) ≥12,500 (highly active)[35].

International Physical Activity Questionnaire (IPAQ)

The IPAQ long version will be self-administered during the first visit at less than 12 weeks gestation in the first trimester and again between 20-24 weeks gestation in the second trimester. It is a set of 4 questionnaires assessing 5 activity domains (occupation, transportation, household, leisure, and sedentary) independently in the past 7 days, and may be administered via self or telephone[42]. Well-established and validated in adults aged 15-69 years, it is available in both English and Chinese[43,44]. It has been used in studies involving pregnant women[29,45].

Data will be reported as continuous and categorical variables. Continuous variables include median MET-minutes per week (MET-min/wk) and interquartile ranges computed for each domain, subdomain (walking, moderate-intensity PA and vigorous-intensity PA) and overall total PA. MET or metabolic equivalent is a unit that measures energy expenditure in multiples of the resting metabolic rate[46]. Categorical variables include classification into low, moderate, high levels of PA according to the IPAQ scoring protocol.

Medical record data

Additional data to be collected include ethnicity, weight changes during pregnancy, weight at 6 weeks post-delivery, obstetric outcomes of GDM, GH, preeclampsia and IUGR, and neonatal outcomes comprising APGAR scores, preterm birth, macrosomia, and neonatal hypoglycemia.

Participant feedback form

After the end of 20 weeks gestation, experience with the activity tracker and mobile application in terms of usability and troubleshooting will be evaluated. Compliance level will be quantified by number of days per week.

Statistics

Descriptive statistics of PA levels in the 1st and early 2nd trimester will be presented. Categorical variables will be presented as n (%) while continuous variables will be presented

as mean (SD) or median (IQR). Mean steps per day and median MET-minutes per week between semesters will be compared using paired Student's t-test and Wilcoxon signed-rank test respectively. McNemar's test will be used to compare sedentary behavior between semesters. Similar tests will be employed to assess for a difference in PA levels between weekdays and weekends.

Binary logistic regression will be used to evaluate the association of early pregnancy PA with GDM and/or GH. Crude (unadjusted) and adjusted regression models will be included. Potential confounders will be identified a priori based on literature review and controlled for in the regression analyses. Potential interactions between covariates and early pregnancy PA will be tested using cross-product terms. Secondary analyses on the bio-socio-demographic factors associated with sedentary behavior, as well as the association between early pregnancy PA level and maternal weight at 6 weeks post-delivery, will follow the methods of the primary analyses, but are exploratory having not been powered to formally test the hypotheses. All regression analyses will be presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Statistical analyses will be performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, N.Y., USA). *P* values of <0.05 will be considered statistically significant.

Safety parameters

Adverse effects and device monitoring will be carried out at the subsequent 4-weekly routine prenatal visits. Any adverse skin reaction to the wristband will be recorded. Participation will be stopped at any time the Principal Investigator decides that continuing on could be harmful to the participant.

Data management

All data will be coded for confidentiality. Hardcopy data will be stored at the research site under lock and key. Electronic data can only be accessed and retrieved from the secured website by the participant and research team. Electronic data will be exported on a fortnightly basis. All data obtained will be entered into and stored on the institution Research Electronic Data Capture (REDCap) system, a centralised secured data management server with password access. Data integrity monitoring will be carried out monthly by the principal investigator and co-investigators if deemed necessary.

Patient and Public Involvement

Patients and the public were not involved in the development of the research question and outcome measures.

Ethics and dissemination

Ethical approval was obtained from the Centralised Institutional Review Board of SingHealth (reference 2017/2836). Informed written consent will be sought from all participants.

Results from this study will be submitted to the funding organization and peer-reviewed journals for consideration of publication both online and in print. Results will also be presented at relevant meetings, conferences and medical forums in either oral or poster formats.

Conclusion

The I-ACT study aims to be the first comprehensive study objectively evaluating the PA levels and patterns in early pregnancy, and their association with GDM and/or GH in the multi-ethnic population of Singapore. In addition to addressing these important scientific knowledge gaps, from a clinical perspective, the study itself may increase awareness of PA during early pregnancy while demonstrating the potential of wearable activity trackers as an objective measure of PA in health research. More importantly, we hope the results of the study facilitate the identification of high-risk mothers-to-be for targeted intervention, and help formulate strategies for interventional efforts.

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Author statement

MC was involved in all aspects of the study from conception, design, recruitment and manuscript writing. KHT and SBA provided critical review of the design and writing. As Principle Investigator, SBA takes overall responsibility for the work. All authors agree to be accountable for their work.

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Conflict of interests

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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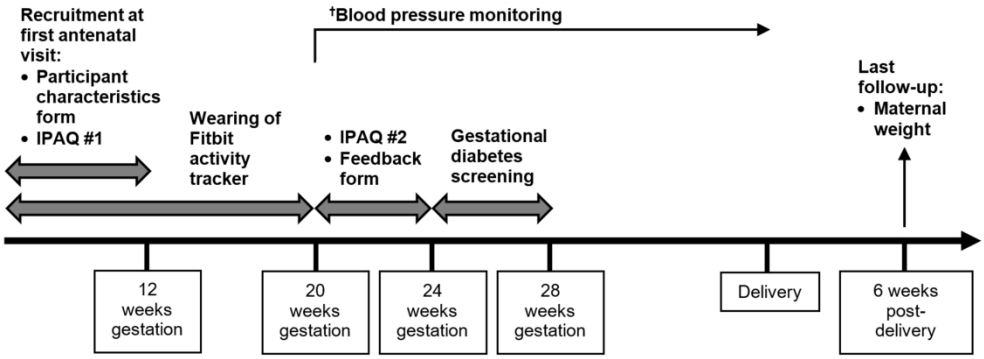
Figure Legend

Figure 1. Timeline of the I-ACT prospective cohort study.
†Participants will continue to attend routine antenatal visits throughout the study period during which blood pressure monitoring will be done.



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