BMJ Open

Study of How Adiposity in Pregnancy has an Effect on outcomeS (SHAPES): protocol for a prospective cohort study

Nicola Heslehurst,[1] Raya Vinogradov,[1,2] Giang T Nguyen ,[1] Theophile Bigirumurame ,[1] Dawn Teare,[1] Louise Hayes,[1] Susan C Lennie,[1] Victoria Murtha,[2] Rebecca Tothill,[2] Janine Smith,[3] John Allotey ,[4,5] Luke Vale[1]

To cite: Heslehurst N, Vinogradov R, Nguyen GT, *et al*. Study of How Adiposity in Pregnancy has an Effect on outcomeS (SHAPES): protocol for a prospective cohort study. *BMJ Open* 2023;**13**:e073545. doi:10.1136/bmjopen-2023-073545

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-073545).

Received 09 March 2023
Accepted 17 August 2023

[1]Population Health Sciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
[2]Maternity Services, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[3]Janine Smith Practice, Newcastle upon Tyne, UK
[4]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK
[5]WHO Collaborating Centre for Global Women's Health, Birmingham University, Birmingham, UK

Correspondence to
Nicola Heslehurst;
nicola.heslehurst@newcastle.ac.uk

ABSTRACT

Introduction Maternal obesity increases the risk of multiple maternal and infant pregnancy complications, such as gestational diabetes and pre-eclampsia. Current UK guidelines use body mass index (BMI) to identify which women require additional care due to increased risk of complications. However, BMI may not accurately predict which women will develop complications during pregnancy as it does not determine amount and distribution of adipose tissue. Some adiposity measures (eg, waist circumference, ultrasound measures of abdominal visceral fat) can better identify where body fat is stored, which may be useful in predicting those women who need additional care.

Methods and analysis This prospective cohort study (SHAPES, Study of How Adiposity in Pregnancy has an Effect on outcomeS) aims to evaluate the prognostic performance of adiposity measures (either alone or in combination with other adiposity, sociodemographic or clinical measures) to estimate risk of adverse pregnancy outcomes. Pregnant women (n=1400) will be recruited at their first trimester ultrasound scan (11^{+2}–14^{+1} weeks') at Newcastle upon Tyne National Health Service Foundation Trust, UK. Early pregnancy adiposity measures and clinical and sociodemographic data will be collected. Routine data on maternal and infant pregnancy outcomes will be collected from routine hospital records. Regression methods will be used to compare the different adiposity measures with BMI in terms of their ability to predict pregnancy complications. If no individual measure performs better than BMI, multivariable models will be developed and evaluated to identify the most parsimonious model. The apparent performance of the developed model will be summarised using calibration, discrimination and internal validation analyses.

Ethics and dissemination Ethical favourable opinion has been obtained from the North East: Newcastle & North Tyneside 1 Research Ethics Committee (REC reference: 22/NE/0035). All participants provide informed consent to take part in SHAPES. Planned dissemination includes peer-reviewed publications and additional dissemination appropriate to target audiences, including policy briefs for policymakers, media/social-media coverage for public and conferences for research

Trial registration number ISRCTN82185177.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This research will address the current evidence gap on whether adiposity measures are more accurate than body mass index (BMI) at predicting risk of pregnancy complications, either on their own or combined with other measures.
⇒ This prospective cohort includes the collection of multiple measures of adiposity and pregnancy outcomes, which will enable direct comparison of measures and an exploration of differences in risk prediction across a range of maternal and infant outcomes.
⇒ Extensive patient, public and stakeholder involvement has been carried out at all stages of the study design to improve research quality and strengthen its relevance and impact on maternity services.
⇒ This cohort study is from a single National Health Service Trust in the North East of England, UK, and may not be generalisable to other populations; therefore, we will validate the findings in new populations in a subsequent validation study.
⇒ There are considerations that need to be factored into any policy change recommendations, such as the costs and benefits of implementing adiposity measures or more complex risk predictions models compared with BMI; these will be explored in a subsequent health economics study.

INTRODUCTION

In England and Wales, 22.4% of women have prepregnancy obesity (body mass index, BMI≥30.0 kg/m^2) which equates to approximately 185 000 women per year based on estimated pregnancy rates (approximately 825 000).[1 2] A further 28.5% have an overweight BMI (25.0–29.9 kg/m^2) which is approximately 235 000 women/year.[1 2] Maternal obesity increases the risk of adverse pregnancy outcomes, including gestational diabetes mellitus (GDM), pre-eclampsia, large-for-gestational-age and small-for-gestational-age baby and pre-term and post-term delivery.[3–6] Additionally, women with obesity, and their

children, are more likely to develop obesity and diabetes in the longer term.[3 4 7]

UK guidelines use early pregnancy BMI measured by their general practitioner or midwife in the first trimester as a proxy measure for prepregnancy BMI to identify women who have obesity and to allocate additional antenatal care. This includes consultant-led obstetric and anaesthetic care, additional screening and monitoring such as screening for GDM and growth scans, and delivery in a high-dependency unit.[8 9] Implementation of obesity guidance is a challenge to maternity services due to the high prevalence of maternal obesity, and associated costs.[10–12] A UK study identified that 22% of National Health Service (NHS) Trusts were not adhering to the GDM screening guidelines for women with obesity, and key barriers to adherence were lack of capacity, resource and funding given the high prevalence of maternal obesity.[13] A recent systematic review identified 13 studies exploring the economic costs of maternal obesity,[14] including five from the UK.[11 15–18] The review found that average incremental costs of obesity ranged from €191 to €16 046, with higher costs among studies that included both neonatal and maternal care costs compared with those only reporting either maternal or neonatal costs (€8964 and €1612, respectively).

Identifying which women require additional care due to increased risk based on BMI may not be an efficient use of NHS resources. Many women who have an obese BMI do not develop any pregnancy complications and therefore do not require care offered. A multicentre study among 5628 women from the UK, Ireland, New Zealand and Australia reported that 47% of pregnant women with an obese BMI had an uncomplicated pregnancy (defined a normotensive pregnancy, >37 weeks gestation, live birth, not small for gestational age and no other significant pregnancy complications) and 53% developed complications.[19] Pregnancy complications also occurred in other BMI groups: 42% of women with an overweight BMI, 33% of women with a recommended BMI and 38% of women with an underweight BMI.[19] In the NHS context, based on current conception rates and maternal obesity prevalence, this prevalence of uncomplicated pregnancies would translate to approximately 87 000 women with an obese BMI each year who are not at increased risk of complications, yet receive additional care. The prevalence of women with an overweight BMI who do develop complications (that are usually associated with obesity) equates to approximately 136 000 women/year who would benefit from additional care but are not eligible based on their BMI. The similarity in numbers of women with an obese BMI who receive care but do not need it, and women with an overweight BMI who require additional care but do not receive it, suggests that more accurate targeting would have minimal net impact on the total cost of providing care but would improve pregnancy outcomes for women and their babies.

One potential reason for the inability of BMI to accurately determine which women will develop complications in pregnancy relates to the high variation in individual phenotype.[20] This makes BMI a poor predictor of adiposity-level and risk, especially among women and some ethnic groups.[21] A meta-analysis of studies in non-pregnant populations shows that using obese BMI criteria only identifies 50% of adults with excess adiposity, as BMI cannot distinguish between fat mass and lean mass, whereas measures of body fat distribution can better distinguish individuals' mortality and cardiometabolic risk.[22 23] This proportion is similar to that observed for women who do not have an obese BMI in pregnancy yet develop complications; these women may have excess adiposity not identified by BMI. Two recent systematic reviews and meta-analysis identified 70 observational studies reporting associations between maternal early-pregnancy adiposity and maternal health outcomes[5] and 34 reporting infant outcomes.[6] However, a limitation of the existing evidence-base is the focus on single or few measures of adiposity and/or pregnancy outcomes within each data set. This makes it challenging to compare the usefulness of different adiposity measurements for predicating the range of pregnancy outcomes usually associated with obesity. A more comprehensive cohort study including multiple measures and outcomes would enable these direct comparisons between adiposity measures, and with BMI, in the same population of women.

Failure to accurately predict which women are at risk of adverse pregnancy outcomes may result in harm for the mothers and babies and increase healthcare costs. Furthermore, inaccurate risk communication can increase anxiety and distress for women.[24] There is an urgent need to identify whether there are measures of adiposity with greater sensitivity and specificity than BMI to inform targeted antenatal care, to improve health of women and babies and make a better use of NHS resources. This prospective cohort study will measure adiposity in early pregnancy to explore the ability of these measures to predict adverse pregnancy outcomes. A range of potential measures exist which use anthropometry (eg, waist circumference, neck circumference and skinfold thickness), imaging such as ultrasound or MRI scans (eg, to measure subcutaneous and visceral fat) and bioelectrical impedance (eg, to measure body fat). However, some measures such as MRI scans and bioelectrical impedance are impractical for implementation into routine pregnancy care due to costs and stringent measurement protocols. Therefore, this study will focus on adiposity measurements that are feasible to implement in routine NHS maternity care.

Aim and objectives

The aim of this cohort study is to evaluate the prognostic performance of single adiposity measures or a multivariable model to estimate risk of adverse pregnancy outcomes (ie, a risk prediction development study).

The objectives of this prognostic factor and model developmental study are as follows:

1. To identify the prognostic value of single adiposity measures for predicting adverse maternal, fetal and neonatal outcomes (for each outcome of interest separately, and as a composite outcome).
2. To develop a prognostic model to investigate the effect of including multiple adiposity, sociodemographic and clinical predictors on the accuracy of predicting outcomes.
3. To test the predictive performance of the prognostic measures/models using calibration, discrimination and internal validation techniques.

METHODS AND ANALYSIS

Study design and setting

This is a prospective observational cohort study in pregnant women. The setting is the maternity unit at The Newcastle upon Tyne Hospitals NHS Foundation Trust (NUTH) where women attend for their first trimester ultrasound dating scan conducted at 11^{+2} to 14^{+1} weeks' gestation.

Study participants

Pregnant women are recruited at their dating scan appointment, starting from April 2022, and we will continue recruitment until sample size achieved. Baseline adiposity measures and other potential predictor variables of interest for a multivariable model (including clinical and sociodemographic data) will be collected from women at this time, or from routine hospital records. Pregnancy outcomes will be collected from routine hospital records after delivery.

Inclusion and exclusion criteria

Inclusion criteria are women with a singleton pregnancy, ≥18 years of age, attending their dating scan between 11^{+2} and 14^{+1} weeks gestation, with a planned delivery at the recruiting NHS Trust. Women will be excluded if they are unable/unwilling to give informed consent to participate, have a miscarriage prior to the dating scan, have an Early Pregnancy Assessment Clinic or accident and emergency visit relating to their pregnancy with a recorded adverse outcome (eg, miscarriage) or are identified as having twin or higher order pregnancy at the time of the dating scan. Due to small numbers of women with twin or higher order pregnancy and different levels of risk to singletons, the study is not powered for this population.

Recruitment procedure

The recruitment procedure is embedded into routine processes and care pathways as much as possible. The process of contacting women for study recruitment is detailed in figure 1. This involves the clinical teams sending a study letter to women referred to the maternity unit for their dating scan (either by post, email or the e-patient record App Badger Notes which has a notification system to alert users to the letter) (see online supplemental material 1). The reproductive health clinical research team (including clinical trial associates, midwives, nurses and radiographers) will phone the women to book their routine dating scan appointment and discuss the SHAPES (SHAPES, Study of How Adiposity in Pregnancy has an Effect on outcomeS) study to enquire whether they might be interested in taking part, using a script to ensure uniformed information provision. Those interested will be booked into the research clinic for their dating scan and will be sent the detailed participant information sheet (online supplemental material 2). Women will be asked to provide written informed consent (online supplemental material 3) on the day of their scan appointment, following their dating scan being completed and checks for eligibility (ie, singleton viable pregnancy within the required gestation). Additionally, some women may be approached on arrival for their routine scan appointment with an offer to participate in this study and the informed consent process will be followed. Women will be offered three printed pictures of their baby from their scan appointment with a framed mount as a thank you gift for taking part in the study. They can also opt into taking part in a prize draw to win one of the 40 available £100 gift vouchers. Finally, we will also promote the study via a website (https://research.ncl.ac.uk/shapes/) and

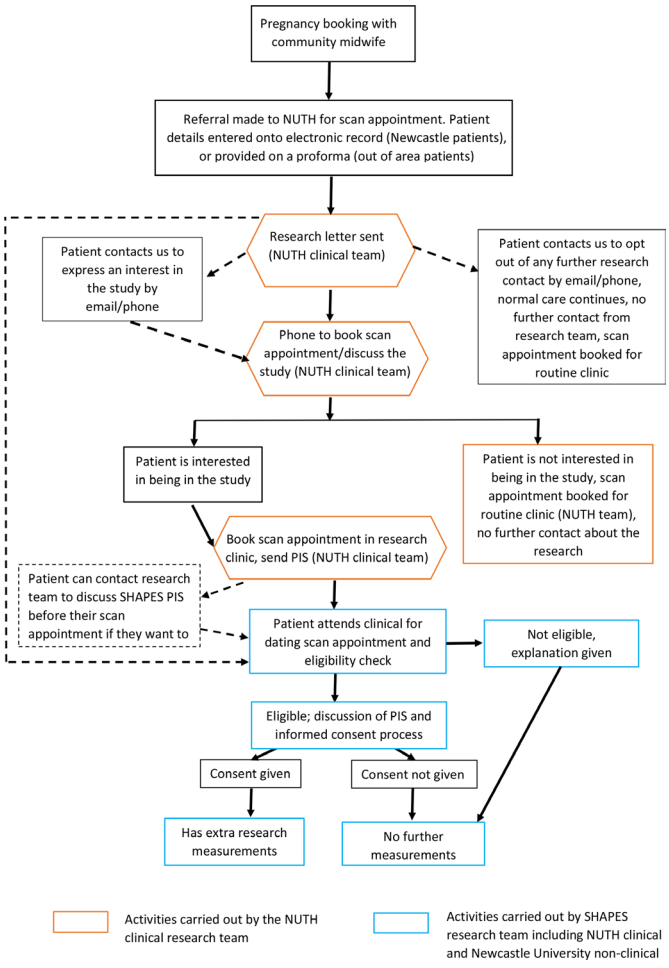

Figure 1 Study recruitment procedure. NUTH, Newcastle Hospitals NHS Foundation Trust; SHAPES, Study of How Adiposity in Pregnancy has an Effect on outcomeS.

social media (the Newcastle Maternity Voices Partnership Facebook page and Connie e-midwife website) to provide an additional opportunity for any eligible women to enquire about the research directly. Any women who do not provide informed consent on the day of their scan appointment will have their routine dating scan carried out, but no additional measurements for the SHAPES cohort study.

We will continuously monitor the recruitment of SHAPES participants in relation to how representative they are of the background maternity population in relation to maternal BMI, age, ethnic group and deprivation. If there are any concerns relating to the recruitment strategy resulting in a biased sample, we will explore alternative strategies with the patient and public involvement (PPI) group.

Sample size

A sample of 1400 women will be recruited to the study. The sample size was based (at the time of grant application) on the 'rule of thumb' that 10 events (cases of the outcome) were required for each variable included in a multivariable model to predict an outcome. However, recent developments in prognostic model research allowed us to confirm the above sample.[25–27] The sample size calculation is based on a maximum of seven candidate variables that are associated with both maternal obesity and adverse pregnancy outcomes (online supplemental material 4) and the least common pregnancy outcome, which is pre-eclampsia (estimated prevalence of approximately 5%–6% of pregnancies in the UK at the time of developing the protocol).[28] This number of candidate variables is similar to previously published validated prognostic models in pregnancy including between 1 and 7 predictor variables.[29–32] Targeting a shrinkage factor of ≤10% and C-index equal to 80%, we would need a minimum sample of 980 participants for a new model development for pre-eclampsia. Given that other outcomes are more prevalent compared with pre-eclampsia, they would require sample sizes lower than the above figure.

Data collection

Participants' dating scans will be performed by qualified trained research sonographers who are part of the usual clinical care team. Once viability of the pregnancy and normal fetal anatomy is confirmed, the additional ultrasound adiposity measures needed for the study will be performed by the study sonographer. The remaining data collection will be performed by a trained member of the research team.

The methods of adiposity measurement are detailed in table 1. Ultrasound scans of subcutaneous and visceral abdominal fat volume will be performed using a GE E8 ultrasound machine (GE Healthcare Austria, GmbH & Co OG) with 2.3–8.4 MHz curvilinear probe. Methods described by Martin *et al*[33] will be used to obtain the measurement. Ultrasound settings and patient position will be standardised to ensure consistency of the procedure. Furthermore, image capture will be standardised for breathing movements (on expiration) and bladder filling. Midline transverse section of the maternal abdomen will be obtained approximately 1 cm superior to the umbilicus to allow visualisation of the transverse section of the abdominal aorta at the far field of the screen. The mean of three consecutive measurements will be employed in the analysis. In addition to the above measurements of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT), an alternative method of measuring these by ultrasound will be deployed to establish optimal methods for future implementation. SAT and VAT will be measured at the sagittal plane of xiphisternum as described by Cremona *et al*.[34] All study sonographers will receive bespoke theoretical and practical training developed locally based on the described methodological literature before data collection commences. In a small subset of participants (n=25), paired and blinded measurements will be repeated by a second operator. Agreement between sonographer measurements will be assessed by calculating intraclass correlation coefficients and Bland Altman plots will be constructed for each measurement types for trends.

All anthropometry measurements will be taken directly on the skin (unless otherwise specified in table 1) on the right side of the body unless impracticable due to injury, in which case the left side may be used. All anthropometric measurements will be taken by individuals who have received anthropometry training following the measurement protocols detailed by the International Society for the Advancement of Kinanthropometry (ISAK)[35] by an ISAK level 3 instructor anthropometrist. Inter-rater reliability will be estimated following ISAK recommendations for calculating technical error of measurements and intraclass correlation coefficients. Measurements will be taken in duplicate, and a third measurement taken if the difference between the first two measures is greater than 5% for skinfolds or 1% for all other measures. If two measures are taken, the mean value will be used in data analysis. If three measures taken, the median value will be used.

Adverse outcomes of interest are shown in table 2 and will be extracted from routine electronic patient medical records. Quality checks will include interrogating the data for missing, unrealistic or inconsistent data, and the clinical research team will resolve these through full medical record review. Adverse outcomes were selected based on maternal obesity evidence-base of risks, and two systematic reviews exploring associations between maternal adiposity and health outcomes,[5 6] and reviewing what data were routinely recorded in maternity patient records. Additional outcome measures considered important for clinical practice and for patients were suggested and included by the external steering group consisting of PPI members, academics and clinical (midwifery, obstetrics and sonography) representatives.

A number of sociodemographic and clinical variables associated with adverse pregnancy outcomes will be

Table 1 Methods of adiposity measurement

Adiposity measure	Measurement
Subcutaneous adipose tissue*	Midline transverse section of the maternal abdomen, approximately 1 cm above the umbilicus from outer border of the subcutaneous fat layer to the outer border of rectus abdominus at the level of linea alba
Visceral adipose tissue*	Midline transverse section of the maternal abdomen, approximately 1 cm above the umbilicus from the inner border of rectus abdominus at the level of linea alba to the anterior wall of the aorta
Preperitoneal subcutaneous adipose tissue*	Sagittal plane of xiphisternum from the lower border of the cutaneous layer to the upper border of the linea alba
Preperitoneal visceral adipose tissue*	Sagittal plane of xiphisternum from the lower border of linea alba to the upper border of the liver capsule
Waist circumference†	Narrowest point of the abdomen between the lower costal (10th rib) border and the top of the iliac crest, perpendicular to the long axis of the trunk, at the end of normal expiration and with the abdominal muscles relaxed, to the nearest 0.1 cm
Hip circumference†	Greatest posterior protuberance of the buttocks, perpendicular to the long axis of the trunk, with the gluteal muscles relaxed and the feet together, over light clothing and to the nearest 0.1 cm
Height†	To the nearest 0.1 cm with shoes removed and the participant's head positioned in the Frankfort plane
Weight†	In light clothing to the nearest 100 g
Neck circumference	Immediately superior to the thyroid cartilage and perpendicularly to the long axis of the neck with the head in the Frankfort plane, to the nearest 0.1 cm
Mid upper arm circumference	Midpoint of the upper arm between the acromiale and radiale, perpendicular to the long axis of the arm, to the nearest 0.1 cm
Skinfold thickness‡	Subscapular, triceps, biceps, iliac crest and supraspinale measured using Harpenden skinfold callipers, to the nearest 0.1 mm

*Total adipose tissue will be calculated as a sum of subcutaneous and visceral adipose tissue.
†Waist-to-hip ratio, waist-to-height ratio, BMI, Body Adiposity Index, A Body Shape Index (ABSI), Hip Index, Weight-Adjusted Waist Index, Body Roundness Index, Total abdominal fat, Abdominal Volume Index, Conicity Index, estimated total body fat, Relative fat Mass, Clínica Universidad de Navarra-Body Adiposity Estimator (CUN-BAE) and body fat percentage will be calculated from these measurements.
‡Sum of skinfolds will be calculated using five skinfold measurements.

collected, as well as data to inform subsequent health economics analysis (eg, place of delivery, length of inpatient stay and maternal medications use) and any reason for loss to follow-up (eg, late miscarriage, stillbirth or participant moving to another area) (online supplemental material 4).

Data management

Participant identifiable information will be handled in line with General Data Protection Regulation (GDPR) 2018 principles. Initial data collection and storage will be via Research Electronic Data Capture (REDCap), a password-protected database. Data will be stored on the NHS secure server under Caldicott approval until recruitment is complete. At the end of the recruitment period, data will be anonymised using a unique identifier for each participant. Following completion of all follow-up data collection, anonymised electronic research data will be transferred to a Newcastle University secure server for analysis. If a participant is withdrawn from the study, the data collected up to that point will be kept to compare the characteristics of withdrawals to non-withdrawals, but not further analysis will be conducted. No personal identifying information will be presented in the study outputs.

Analysis

The aim of the analysis is to explore if any single adiposity measure taken in this study performs better than BMI in terms of predicting women who develop an adverse pregnancy outcome. Each adiposity measure will be assessed individually and compared with BMI (ie, unadjusted models). Where possible, secondary subgroup analysis will be carried out for different ethnic groups. If no individual measure performs better than BMI (ie, current practice), we will build multiple logistic regression model(s) by adding all the prespecified predictors/covariates for the analysis of each outcome separately (ie, the adjusted model). A backward selection method will be used to eliminate unimportant predictors/covariates. A backward elimination may lead to a more parsimonious model which is therefore easier to implement in clinical practice than a full model. We will compare these models to the unadjusted BMI model to identify which has the best predictive performance measures. Wherever possible, we will retain continuous candidate predictors in their

Table 2 Pregnancy outcomes for the SHAPES cohort

Outcomes	Definition
Maternal outcomes	
Gestational diabetes*	Fasting plasma glucose level of ≥5.6 mmol/L or 2 hour plasma glucose level of ≥7.8 mmol/L
Gestational hypertension	Blood pressure≥140/90 mm Hg on two occasions at least 4 hours apart after 20 weeks' gestation
Pre-eclampsia	New onset of hypertension (>140 mm Hg systolic or >90 mm Hg diastolic) after 20 weeks of pregnancy with a new onset of proteinuria or/and maternal organ dysfunction or/and uteroplacental dysfunction. Early onset defined as onset of pre-eclampsia before 34 weeks gestation
Induction of labour	Non-surgical treatment to induce the labour
Caesarean section	Surgical delivery of baby (emergency or elective)
Instrumental delivery	Assisted birth when forceps or a ventouse suction cup is applied
Retained placenta	As reported in medical records
Maternal infection	As reported in medical records
Postpartum haemorrhage (PPH)	Third stage of labour and immediate postpartum period, measured in mL blood loss
Maternal length of stay in hospital	From admission date for any stay resulting in delivery to date of discharge
Infant outcomes	
Fetal growth	Measured at second and third trimester scans, including: Second trimester scan: fetal head circumference; fetal abdominal circumference; fetal femur length; estimated fetal weight Hadlock Third trimester scan: abdominal circumference; femur length; estimated fetal weight Hadlock; umbilical artery PI; end diastolic flow; Amniotic Fluid Index
Preterm birth	Birth before 37 weeks gestation
Late-term birth	Pregnancy that extends over 41 weeks gestation
Large for gestational age	Birth weight above the 90th centile for gestational age and sex on INTERGROWTH chart
Small for gestational age	Birth weight below the 10th centile for gestational age and sex on INTERGROWTH chart[46]
Apgar score	1 and 5 minutes
Neonatal jaundice	As reported in medical records
Neonatal respiratory distress (requiring resuscitation)	Any of the following: cords visualised meconium seen; cord visualised no meconium; facial air; facial oxygen; mucus extraction or suction; positive pressure by bag or mask; positive pressure by endotracheal tube
Feeding method	First feed: artificial; breast mother; breast donor; breast and artificial; no feed given Feed method at discharge: breastfeeding or artificial feed or both breast and artificial
Infant admission to specialist care	Admission to neonatal special care baby unit or intensive care unit, high-dependency care, transitional care; length of stay if admitted

*Note this outcome can only be determined for those women who have had an oral glucose tolerance test.
SHAPES, Study of How Adiposity in Pregnancy has an Effect on outcomeS.

continuous form to avoid statistical power loss.[36] In case a linear association between a continuous predictor and the outcome is doubtful, we will explore flexible parametrisation of the predictor to study non-linear associations. To this end, fractional polynomials and restricted cubic splines will be used, and we will select the one giving best fit (using appropriate statistical measures).[36]

The apparent performance of the developed model(s) will be summarised using calibration, discrimination and internal validation analyses.[37] Calibration determines performance in terms of the agreement between the probability of developing the outcome as estimated by the measure/model, and the observed outcome frequencies. Discrimination is the measure of the model's ability to distinguish between individuals who develop the outcome or not (ie, a higher probability assigned to the individual who develops the outcome compared with an individual who does not. This will be assessed using the c-index (equivalent to the area under the receiver operating characteristic curve). Any missing values will be assumed to be missing at random and multiple imputation will be implemented using 20 imputations.[38] Calibration and discrimination of the developed model(s) will be summarised in the development data sets (averaged over imputation data sets). Calibration will also be assessed graphically.[39]

The model(s) will be internally validated using bootstrap resampling method in order to quantify the degree of optimism due to overfitting[40 41] and to derive optimism-adjusted indices of discrimination (c-index) and calibration (calibration slope). Two hundred bootstrap samples will be used.[41 42] Optimism is expected when measures/models are applied to the same data set used for development, as they have been developed to achieve the best fit for that specific data set (ie, overfitting). Statistical techniques (eg, bootstrapping) can quantify the potential for overfitting, and provide adjustment estimates (eg, shrinkage factor) to reflect the prognostic performance in a new dataset/population.

Patient, public and stakeholder involvement

Extensive PPI and stakeholder involvement has been carried out for this research. Pregnant and postnatal women, clinical stakeholders (obstetricians, midwives and sonographers) and the NIHR Research Design Service North East and North Cumbria consumer panel were involved in the development of the proposed research funding application, protocol, and in planning how to embed PPI into this research.

PPI consultations were carried out with pregnant and postnatal women attending a community group. Discussion topics included acceptability and timing of adiposity measurements; reviewing the plain English and PPI sections of the funding application; discussing how to communicate research to pregnant women and wider public; future PPI involvement in the research; the process of recruitment involving sending letters and follow-up phone calls; the provision of thank you gifts to research participants and decision to include a prize draw; and reviewing the PIS, recruitment letters and social media advertisements. PPI members strongly thought this research was a priority and we addressed issues raised during these discussions by amending our planned research methods, such as the recruitment strategy. We have planned consultations with pregnant and postnatal women to be embedded throughout the research, as well as having PPI representatives on the steering group and as a coinvestigator (JS).

Key discussion points with clinical stakeholders included considering the effect of existing guideline interventions for women with a BMI≥30 kg/m^2 as women will continue to receive this routine care during the research time period; recruitment and measurement logistics in the routine antenatal scan clinics; equipment and training required for sonographers to carry out the additional ultrasound measurements and processes for recruitment. Clinical stakeholders will continue to be involved in the steering group.

ETHICS AND DISSEMINATION

This is a low risk, observational study. This study has been reviewed and given a favourable opinion by the North East—Newcastle & North Tyneside 1 Research Ethics Sub-Committee and the Health Research Authority. Caldicott and local R&D approvals will be in place before the study begins. The study sponsor is Newcastle upon Tyne Hospitals NHS Foundation Trust. All SHAPES participants will be required to give informed consent before taking part in the research. Potential participants will receive a copy of the participant information sheet and consent form, and these will be discussed with a member of the research team when they attend for their dating scan appointment (figure 1). Those consenting to participate in SHAPES will have their routine dating scan and SHAPES additional measurements carried out at their appointment. Those not consenting at this stage will have their routine dating scan and no further measurements.

The SHAPES study is part of a wider NIHR Advanced Fellowship research programme. The planned research programme includes validating the results of the SHAPES cohort study in a subsequent study, using individual participant data (IPD) meta-analysis methods. We have identified eligible studies for the IPD study in two systematic reviews[5 6] as well as a search for registered cohort studies as described in the PROSPERO registration,[43] and invited authors to join an international IPD collaboration. An economic evaluation of implementing an alternative approach to risk prediction into routine NHS maternity care is also planned. A decision model approach will be used and the data required for the model will come from the SHAPES study (eg, the performance of the risk prediction approaches), expert opinion (eg, costs of using the risk prediction tools) and from the literature (eg, relating to potential implications for longer term maternal and infant outcomes). The analysis will compare the costs of changing routine practice to implement adiposity measures/risk prediction models if they are shown to be better at predicting risk than current practice using BMI, and the cost implications of changes to health outcomes following changes in the targeting of antenatal care. In this study, we can also explore the health economics implications of implementation of more complex versus simpler risk prediction models. The findings of this will also be used to help inform policy recommendations. All research will be published in peer-reviewed journals and reported using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[44] and the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines.[45] Further dissemination will be audience appropriate, for example utilising research briefs, policy briefs, media coverage and stakeholder and participant communication to achieve this goal. The target audiences for this work are health professionals and their affiliated organisations, pregnant women and their families, maternity managers and commissioners of services, national and international policy makers, wider public, third sector, and other researchers.

Acknowledgements We thank the Chair of the SHAPES Steering Group Dr Vikki Smith, and additional members Professor Judith Rankin, Professor Marian Knight,

Professor Stephen Robson, Dr Kenneth Hodson for their contribution on advising and guidance to the Study Management Group on the planning, delivery, evaluation and dissemination of the project; as well as the SHAPES clinical team: Marc Davies, Gayle Gills, Jessica Bell, Sophie Fowler, Amy Lennox and Brandon Huntsman. We also thank all members of the Patient and Public Involvement groups who actively contribute to the design and conduct of the SHAPES research.

Contributors NH and LV developed the concept for this research and secured funding. All authors contributed to the development of the protocol and ethics application. RV, VM and RT developed the clinical implementation of the research, including the process of recruitment and logistics of measurements being carried out in routine clinics. TB and DT provided statistical methods input. GTN and NH drafted this manuscript and all authors contributed to reviewing and editing.

Funding This study is funded by the NIHR Academy (CDF-2018-11-ST2-011) through an Advanced/Career Development Fellowship. TB is funded by the NIHR Applied Research Collaboration North East and North Cumbria (Grant/Award Number: NIHR200173).

Disclaimer The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Giang T Nguyen http://orcid.org/0000-0003-4612-8301
Theophile Bigirumurame http://orcid.org/0000-0003-2387-4918
John Allotey http://orcid.org/0000-0003-4134-6246

REFERENCES

1 NMPAProjectTeam. National maternity and perinatal audit: clinical report 2022. Based on births in NHS maternity services in England and Wales between 1 April 2018 and 31 March 2019. 2022. Available: https://maternityaudit.org.uk/FilesUploaded/Ref%20336%20NMPA%20Clinical%20Report_2022.pdf
2 Office for National Statistics. Conceptions in England and Wales: 2021. 2021. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/conceptionandfertilityrates/bulletins/conceptionstatistics/2021#:~:text=2.-,Conceptions%20numbers%20and%20rates,births%20also%20increased%20in%202021
3 Marchi J, Berg M, Dencker A, *et al*. Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews. *Obes Rev* 2015;16:621–38.
4 Heslehurst N, Vieira R, Hayes L, *et al*. Maternal body mass index and post-term birth: a systematic review and meta-analysis. *Obes Rev* 2017;18:293–308.
5 Heslehurst N, Ngongalah L, Bigirumurame T, *et al*. Association between maternal adiposity measures and adverse maternal outcomes of pregnancy: systematic review and meta-analysis. *Obes Rev* 2022;23:e13449.
6 Nguyen G, Hayes L, Ngongalah L, *et al*. Association between maternal adiposity measures and infant health outcomes: a systematic review and meta-analysis. *Obes Rev* 2022;23:e13491.
7 Godfrey KM, Reynolds RM, Prescott SL, *et al*. Influence of maternal obesity on the long-term health of offspring. *Lancet Diabetes Endocrinol* 2017;5:53–64.
8 NICE. *Obesity: identification, assessment and management. Clinical guideline CG189*. London: NICE, 2014.
9 CMACE/RCOG. *CMACE/RCOG joint guideline: management of women with obesity in pregnancy*. Centre for Maternal Child Enquiries Royal College of Obstetricians Gynaecologists, 2010.
10 Aughey H, Blotkamp A, Carroll F, *et al*. National maternity and perinatal audit: clinical report 2019. based on births in NHS maternity services between 1 April 2016 and 31 March 2017. 2019.
11 Denison F, Norrie G, Graham B, *et al*. Increased maternal BMI is associated with an increased risk of minor complications during pregnancy with consequent cost implications. *BJOG* 2009;116:1467–72.
12 Lenoir-Wijnkoop I, van der Beek EM, Garssen J, *et al*. Health economic modeling to assess short-term costs of maternal overweight, gestational diabetes, and related macrosomia - a pilot evaluation. *Front Pharmacol* 2015;6:103.
13 Bell R, Hayes L, Pasecinic N, *et al*. Implementation of national screening guidelines for gestational diabetes: a national survey of maternity units in England. *Diabetes Res Clin Pract* 2018;146:58–66.
14 Moran PS, Wuytack F, Turner M, *et al*. Economic burden of maternal morbidity–a systematic review of cost-of-illness studies. *PLoS One* 2020;15:e0227377.
15 Solmi F, Morris S. Overweight and obese pre-pregnancy BMI is associated with higher hospital costs of childbirth in England. *BMC Pregnancy Childbirth* 2018;18:253.
16 Morgan KL, Rahman MA, Hill RA, *et al*. Obesity in pregnancy: infant health service utilisation and costs on the NHS. *BMJ Open* 2015;5:e008357.
17 Morgan KL, Rahman MA, Macey S, *et al*. Obesity in pregnancy: a retrospective prevalence-based study on health service utilisation and costs on the NHS. *BMJ Open* 2014;4:e003983.
18 Denison F, Norwood P, Bhattacharya S, *et al*. Association between maternal body mass index during pregnancy, short-term morbidity, and increased health service costs: a population-based study. *BJOG: Int J Obstet Gy* 2014;121:72–82.
19 Chappell LC, Seed PT, Myers J, *et al*. Exploration and confirmation of factors associated with uncomplicated pregnancy in nulliparous women: prospective cohort study. *BMJ* 2013;347:f6398.
20 Flegal KM, Kit BK, Orpana H, *et al*. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013;309:71–82.
21 Tanamas SK, Lean MEJ, Combet E, *et al*. Changing guards: time to move beyond body mass index for population monitoring of excess adiposity. *QJM* 2016;109:443–6.
22 Després J-P. Body fat distribution and risk of cardiovascular disease: an update. *Circulation* 2012;126:1301–13.
23 Nazare J-A, Smith J, Borel A-L, *et al*. Usefulness of measuring both body mass index and waist circumference for the estimation of visceral adiposity and related cardiometabolic risk profile (from the INSPIRE ME IAA study). *Am J Cardiol* 2015;115:307–15.
24 Heslehurst N. "Identifying 'at risk' women and the impact of maternal obesity on national health service maternity services". *Proc Nutr Soc* 2011;70:439–49.
25 Ahmed I, Debray TPA, Moons KGM, *et al*. Developing and validating risk prediction models in an individual participant data meta-analysis. *BMC Med Res Methodol* 2014;14:3.
26 Riley RD, Ensor J, Snell KIE, *et al*. Calculating the sample size required for developing a clinical prediction model. *BMJ* 2020;368:m441.
27 Riley RD. Correction to: minimum sample size for developing a multivariable prediction model: part II-binary and time-to-event outcomes by Riley RD, Snell KI, Ensor J, et al. *Stat Med* 2019;38:5672.
28 Tommys.org. *Pre-eclampsia statistics*. 2018.
29 Chandrasekaran S, Bastek JA, Turitz AL, *et al*. A prediction score to assess the risk of delivering a large for gestational age infant among obese women. *J Matern Fetal Neonatal Med* 2016;29:22–6.
30 Iliodromiti S, Sassarini J, Kelsey TW, *et al*. Accuracy of circulating adiponectin for predicting gestational diabetes: a systematic review and meta-analysis. *Diabetologia* 2016;59:692–9.
31 Cremona A, O'Gorman CS, Ismail KI, *et al*. A risk-prediction model using parameters of maternal body composition to identify gestational diabetes mellitus in early pregnancy. *Clin Nutr ESPEN* 2021;45:312–21.
32 Donovan BM, Breheny PJ, Robinson JG, *et al*. Development and validation of a clinical model for preconception and early pregnancy

risk prediction of gestational diabetes mellitus in nulliparous women. *PLoS One* 2019;14:e0215173.
33 Martin AM, Berger H, Nisenbaum R, *et al*. Abdominal visceral adiposity in the first trimester predicts glucose intolerance in later pregnancy. *Diabetes Care* 2009;32:1308–10.
34 Cremona A, Hayes K, O'Gorman CS, *et al*. Inter and intra-reliability of ultrasonography for the measurement of abdominal subcutaneous & visceral adipose tissue thickness at 12 weeks gestation. *BMC Med Imaging* 2019;19:95.
35 Esparza-Ros F, Vaquero-Cristóbal R, Marfell-Jones M. *International standards for anthropometric assessment*. International Society for the Advancement of Kinanthropometry (ISAK), 2019.
36 Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol* 1999;28:964–74.
37 Moons KGM, Kengne AP, Woodward M, *et al*. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio) marker. *Heart* 2012;98:683–90.
38 Marshall A, Altman DG, Holder RL, *et al*. Combining estimates of interest in prognostic 498 modelling studies after multiple imputation: current practice and guidelines. *BMC Med Res Methodol* 2009;9:500.
39 Royston P, Moons KGM, Altman DG, *et al*. Prognosis and prognostic research: developing a prognostic model. *BMJ* 2009;338:b604.
40 Collins GS, Reitsma JB, Altman DG, *et al*. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015;162:735–6.
41 Steyerberg EW, Harrell FE Jr, Borsboom GJ, *et al*. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol* 2001;54:774–81.
42 Alonzo TA. Clinical prediction models: a practical approach to development, validation, and updating: by Ewout W. *American Journal of Epidemiology* 2009;170:528.
43 Nguyen G, Allotey J, Vale L, *et al*. Study of how adiposity in pregnancy has an effect on outcome (SHAPES): a systematic review and individual participant data (IPD) meta-analysis. PROSPERO 2022 CRD42022310760. 2022. Available: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022310760
44 von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344–9.
45 Collins GS, Reitsma JB, Altman DG, *et al*. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMC Med* 2015;13:1.
46 Papageorghiou AT, Kennedy SH, Salomon LJ, *et al*. The INTERGROWTH-21St fetal growth standards: toward the global integration of pregnancy and pediatric care. *Am J Obstet Gynecol* 2018;218:S630–40.