PHSI Biostatistics Research Group

Statistical Analysis Plan (SAP) for the SHAPES project

Study of How Adiposity in Pregnancy has an Effect on outcomeS (SHAPES) - Individual Participant Data (IPD) Meta-analysis (MA) Study

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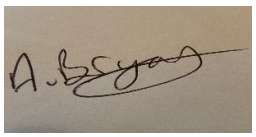
Signature:  **Date**: 14/07/2025

Reviewed and approved by:

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CONTENTS

1. INTRODUCTION

This statistical analysis plan (SAP) provides guidelines for the data analysis to be undertaken for the presentation and publication of the individual participant data meta-analysis (IPD MA) for the SHAPES study. This plan, along with all other documents relating to the analysis of this study, will be stored in a secure place on Newcastle University Teams and network (S) drive.

The SHAPES-IPD MA study builds on the SHAPES Cohort study (risk prediction modelling study) and therefore there is overlap in the SAPs. To avoid duplication of material, the SHAPES-IPD MA SAP will be restricted to information and analyses relevant to this study. The SHAPES-IPD SAP will provide short summaries of the SHAPES Cohort SAP (https://research.ncl.ac.uk/shapes/informationforresearchers/1shapescohortstudy/) in certain sections where appropriate but will mostly cross reference to the SHAPES Cohort working documents. Please refer to the protocol for full details of the SHAPES study including the study population, aims and objectives, details of recruitment associated with the SHAPES Cohort (Heslehurst et al. 2023). Other aspects of the SHAPES Cohort study, its conduct and generic aims and objectives are also provided in full detail in the protocol (version 6.0 27th November 2023), and in Section 1 of the SHAPES Cohort SAP (https://research.ncl.ac.uk/shapes/informationforresearchers/2individualpatientdataipdmeta-analysis/) and in the health economics analysis plan (HEAP)(https://research.ncl.ac.uk/shapes/informationforresearchers/3cost-effectivenessstudy/) upon its completion.

The overarching purpose of the SHAPES-IPD MA is to externally validate the findings of the SHAPES Cohort risk prediction analysis in heterogeneous external populations. This will be achieved in the analyses of individual studies in stage 1 of the SHAPES-IPD MA and will allow exploration of generalisability, and thus to potentially inform whether the Newcastle specific SHAPES Cohort findings could be rolled out to the wider NHS context. A further external validation will then be attempted in stage 2 of the IPA MA where it will be established whether further generalisations and inferences can be made.

The results for the SHAPES-IPD MA will be compared to the results for the SHAPES Cohort study to identify how similar they are in different populations. The potential for overfitting of the original model development will be explored as the risk prediction models were developed to best fit the SHAPES Cohort population

1.1 Background to SHAPES IPD MA

Maternal obesity studies show that populations with a BMI≥30kg/m^2 have an increased risk of multiple pregnancy complications; clinical guidelines therefore use BMI to determine which pregnant individuals receive “high-risk” care. However, extensive research demonstrates BMI poorly predicts obesity-related risk at the individual-level compared with adiposity measures of body-fat distribution (e.g. waist to height ratio), type (e.g. visceral or subcutaneous fat), and amount (e.g. adipose tissue volume or thickness). Risk prediction research can help to identify whether adiposity measures have greater sensitivity and specificity than BMI, which could inform more targeted high-risk care. The SHAPES Cohort is a risk prediction model development study. Any new risk prediction models require validation in external populations before implementation into routine healthcare practice. The SHAPES-IPS MA study aims to externally validate the SHAPES Cohort risk prediction models using data from international and heterogeneous populations.

Scoping work identified that IPD could be realistically obtained, which makes this analysis particularly attractive, as the analyses can be controlled and bias minimised (especially selective reporting of outcomes, confounding and reporting biases). Systematic searches identified 93 studies with relevant early pregnancy adiposity measurements and pregnancy outcome data. We were unable to find working contact details for authors of two studies and got responses from authors of 40 studies. There were 10 that replied that they did not want to collaborate, that they no longer had access to the data to be able to share, could not provide the data to the IPD MA timescale, or the data they held did not meet our inclusion criteria (e.g. adiposity measurements were used prior to conception rather than using early pregnancy measures). There were 19 authors of 20 studies that agreed to collaborate and provide data. One further study author in China was not able to share their IPD (Han et al., 2018); however, they plan to follow the SHAPES-IPD SAP to replicate the analyses in their dataset and share the results for inclusion in stage 2 of the MA. The results of this study will be included if they are provided before the IPD MA is finalised. Sensitivity analyses can be conducted to include any studies reporting aggregate data (in format ready to enter into stage 2 of the MA), but which are not able to contribute IPD. The process of obtaining the IPD was aided by the grant research funding and the cooperation of study personnel. A PRISMA flow chart of study selection process is shown in Appendix 1.

1.2 Why use IPD

The limitations of aggregate data MA have previously promoted the use of IPD MA and methods (Maxwell 2024; Oxman 1995; Stewart 1993; Stewart 1995). Data sharing is now expected within the scientific community and IPD approaches are encouraged. IPD methods can allow participants to be reinstated into the analysis who were originally excluded, help overcome outcome reporting bias (ORB) and facilitate a detailed exploration of participant level covariates and their influence on the effect estimates (Debray 2015; Maxwell 2024; Tierney 2024). Other advantages include more thorough data checking and standardisation of analysis (see details about mapping and data harmonisation in section 2.3). Outcome definitions can be standardised across studies allowing for a more complete analysis (Maxwell 2024; Tierney 2024). An IPD should also allow a more thorough, and potentially a more reliable, analysis of the area under the curve (AUROC) outcomes associated with this SAP. However, the IPD approach is much more resource intensive than a MA using aggregate summary statistics alone (Maxwell 2024).

1.3 Potential advantages of IPD MA

The potential advantages of using an IPD MA will be utilised where possible. This may include attempts in the following areas (Maxwell 2024; Oxman 1995; Stewart 1993; Stewart 1995):

- Use of consistent inclusion and exclusion criteria across studies, and if appropriate reinstate individuals into the analysis who were originally excluded (although this may be difficult in most cohorts).
- Observe and account for missing data at the individual-level (see missing data section 5.2)
- Verify results presented in the original study publications (assuming IPD provided can be matched to that IPD used in the original analyses)

- Use up-to-date follow-up information, potentially longer than that used in the original study publications
- Identify those studies which contain the same or overlapping sets of participants
- Calculate and incorporate results for those missing or poorly reported outcomes and summary statistics across published studies, which may reduce the problem of selective within-study reporting (e.g. of outcomes)
- Calculate and incorporate results for unpublished studies, which may reduce the problem of publication bias
- Standardise the strategy of statistical analysis across studies including the analysis method, how continuous variables are analysed, etc; use more appropriate/advanced methods than primary studies where necessary
- Assess model assumptions in each study (e.g. proportional hazards in Cox regression model)
- Produce estimates adjusted for baseline (prognostic) factors, which may increase power and allow adjustment for confounding factors
- Adjust for consistent baseline (prognostic) factors across studies
- Generate and validate prognostic/prediction models (risk scores), and examine multiple individual-level factors in combination (e.g. multiple adiposity, socio-demographic and clinical factors and their interaction)

The potential disadvantages of conducting an IPD MA were minimised by obtaining grant funding to fund researcher time, advanced statistics, specialised techniques, travel for collaborators meeting and the time-consuming processes (e.g. to obtain, collate, manage IPD). A data harmonisation and mapping process (see section 2.3) will be used to deal with inconsistent variables and data coding used from study to study (Maxwell 2024).

1.4 Biases in IPD MA

An IPD MA should not be viewed as 'gold standard' without considering how IPD studies were chosen. Our inclusion criteria include IPD from both published and unpublished studies, given the fact that there is potential for publication bias (e.g. published studies may have larger effects than unpublished studies) and selection bias (e.g. chosen studies may not be an unbiased sample of all existing studies) (Tierney 2024). The studies identified for inclusion in the IPD were also systematically identified using best practice methods in evidence synthesis (Tierney 2024). IPD was provided by all those studies who agreed to provide data, except for one (Han et al. 2018) where, as noted above, authors have agreed to replicate our stage 1 analyses themselves. A sensitivity analyses will be undertaken for all other studies where only aggregate data are available (see section 5.4), thus minimising availability bias (studies providing their IPD may be systematically different from those refusing) (Maxwell 2024).

1.5 Objectives

The SHAPES-IPD MA aims to evaluate the prognostic performance of adiposity measures in multivariable models (or single adiposity measure depending on results of SHAPES Cohort study) that estimate the risk of adverse pregnancy outcomes.

More specifically, the SHAPES-IPD MA will attempt to externally validate the findings of the SHAPES Cohort risk prediction analysis in heterogeneous external populations. Stage 1 of the IPD MA will explore the generalisability of the findings to potentially inform whether the Newcastle specific SHAPES Cohort findings are applicable the wider UK NHS context. Stage 2 of the IPA MA will attempt to establish whether global generalisations can be made. This will be repeated for the multiple outcomes specified in the various SHAPES-IPD MAs.

2. METHODS

2.1 Identification of eligible studies

The search strategy for identifying eligible studies was prospectively registered on PROSPERO (PROSPERO 2022 CRD42022310760). Two systematic reviews were conducted (Heslehurst et al. 2022, Nguyen et al, 2022) to identify relevant studies using standard evidence synthesis methodology (Tierney 2024). Additional searches to identify unpublished cohorts with the required data used birthcohorts.net, MRC cohort directory, and the International Journal of Epidemiology cohort profiles. Forwards and backwards citation chaining was conducted for all included studies. Study authors were contacted by email with up to 5 reminders, and through their institutions/social media. A SHAPES-IPD collaboration group was formed with study personnel from all included studies (first study group collaborators meeting was conducted in April 2025 in Newcastle, UK).

Study authors were first invited to collaborate in the SHAPES IPD MA from August 2022, with the main deadline to obtain the IPD being end of January 2025 (total duration of 30 months). Consequently, due to the extensive time demands we will not run or update further searches past our original cut off search date.

All eligibility criteria for the SHAPES Cohort study and full details of study selection for the SHAPES-IPD MA is given in the SHAPES protocol (Heslehurst et al. 2023) and Prospero registration (PROSPERO 2022 CRD42022310760).

2.2 Process after receiving IPD

It is important to understand the data (Maxwell 2024) so the research team will check the study protocol of each identified study and decipher the variable codes for each study. Published study results may be replicated to help identify any queries and cross validate data cleaning and analysis assumptions.

Data will be checked, especially to identify extent of any missing participants and queries will be raised where possible. Data will be 'cleaned' and recoded to a consistent format across studies (where necessary and depending on analysis approach). Outcomes will be defined consistently across studies (see section 4) and data analysed according to the pre-specified analyses (see section 5).

2.3 Project management

Details about the wider SHAPES Cohort study timings and roles and other administrative items can be found in the SHAPES Cohort protocol (version 6.0 27th November 2023). Details about any communication with study authors for the SHAPES-IPD MA study will be reported.

Spreadsheets will be created to offer a consistent approach to documenting the SHAPES-IPD MA variables and definitions (master codebook), how each study's variables map to the SHAPES-IPD MA's variables (harmonisation sheet), and the status of each study's dataset in the harmonisation workflow and communication surrounding the data during the harmonisation process (dataset tracking sheet). These spreadsheets are helpful when the harmonisation process is conducted manually (Maxwell 2024). However, the data management and harmonisation of some variables will depend on the results of the analyses specified and performed in the SHAPES Cohort SAP, (https://research.ncl.ac.uk/shapes/informationforresearchers/1shapescohortstudy/) as it is currently unknown exactly which variables will be included in the final risk prediction models

that will be externally validated in the SHAPES-IPD MA study. Some key variables (adiposity measures and GDM – primary outcome) are essential and will be included in the risk prediction models without any selection procedure. Therefore, harmonisation will prioritise these variables in the first instance.

2.3.1 Development of master codebook

A master codebook spreadsheet will be created to record the core variables to which IPD from contributing studies will be harmonised (Maxwell 2024). The template master codebook will include columns for the SHAPES-IPD MA variable names, data types, definitions, outcomes, values, and notes from the harmonisation team (comprised of researchers on the SHAPES Cohort study and the SHAPES-IPD MA collaborating group). The formulas required to derive some adiposity variables is given in Table 1 in section 3.1.

2.3.2 Pre-harmonisation data check of the participant-level data

An initial check of each study's dataset will be made. After the required study documentation has been received and approved, and the study's participation in the SHAPES-IPD MA has been confirmed, the collaborating study team will provide its full de-identified dataset to Newcastle University. Two copies of the dataset will be saved: the original dataset will be stored, with a copy then transformed and harmonised, as necessary.

Data will be evaluated by the SHAPES-IPD study team for clinically implausible values and differences in variables and dataset format and structure across studies in line with our study protocol. When issues arise during the preliminary dataset review, the SHAPES-IPD study team will follow up with the collaborating study team to review and resolve any queries. All data cleaning and harmonisation-related communications will be tracked and any communication with study personnel stored in electronic folders.

2.3.3 Mapping

Before beginning the harmonisation of the study dataset, the SHAPES-IPD study team will review how variables map to the SHAPES-IPD MA master codebook variables. This could include direct communication face to face, logging a call or email correspondence with the collaborating study team for any clarification when required. The harmonisation spreadsheets will be key for the mapping process and will record how each study's variables need to be transformed to correspond to the SHAPES-IPD MA's variables.

2.3.4 Harmonisation

When combining IPD to conduct a MA, it is essential to interpret whether individual variables and measures are similar, both qualitatively and quantitatively (Maxwell 2024). Thus, prior to analysis a process of data harmonisation is required. Ensuring data compatibility and inferential equivalence through harmonisation allows integrating information from different studies/databases and can thereby permit pooling of data from many studies to obtain statistically valid results (Maxwell 2024). It also allows a proper exploration of the similarities and discrepancies across studies, jurisdictions, or countries, and improve the validity and reliability of comparative effectiveness research (Griffith 2013).

The characteristics of collaborating studies will be identified and documented, and all relevant information describing samples, data items, and collection methods, such as data dictionaries or codebooks, questionnaires, and standard operating procedures. This documentation will allow the identification of sources of study heterogeneity and provide the elements required to achieve proper evaluation of the harmonisation potential across

studies (Griffith 2013). Variables from eligible studies will be harmonised with other included IPD datasets.

Any missing data, obvious errors, inconsistencies between variables or outlying values will be queried and rectified through input from the original collaborating study team. A review of how each study's variables map to the IPD-MA master codebook will be made, and harmonisation will be achieved by using the mapping instructions and developing each dataset so that it aligns with what is necessary to undertake the SHAPES-IPD MA.

2.3.5 Post-harmonisation data check

The SHAPES-IPD MA study team will set up a meeting with the collaborating study teams to compare the variables and distributions that result from applying the harmonisation process to the variables in the original dataset to ensure that the data have been appropriately handled and interpreted correctly. A call with the study team is often an efficient way to ensure the study data have been appropriately harmonised (Maxwell 2024). However, although it is more costly, a face-to-face meeting with all study personnel is likely be the most effective form of communication and is therefore planned at the pre-harmonisation stage. Further face-to-face meetings are unlikely to be feasible due to the international nature of the collaboration and time restrictions on the delivery of the final analyses. Therefore, virtual meetings are planned post-harmonisation for any study specific issues.

3. STUDY POPULATION

3.1 Baseline Participant Characteristics

Demographic, clinical and baseline characteristics (e.g. age) will be summarised descriptively and narratively. Characteristics such as ethnicity will be summarised by reporting the number (%) in each category, whereas continuous variables such as age will be reported as mean (SD) and range or median (IQR) as appropriate.

The following baseline variables were collected in the SHAPES Cohort study and will be attempted to be reported across included studies in the IPD MA: [NB Table 1 includes more variables than are likely to be collected across studies and granular category options. The SHAPES-IPD MA will report these variables across studies in the most appropriate and standardised way].

Table 1: Summary of baseline characteristics across studies

Variable	Summary
Socio-demographics	
Age	Age at booking appointment (years)
Parity	Number of previous pregnancies beyond 24 weeks gestation
Ethnic group	White Mixed Asian Black Other
Socio economic measures	As reported
For any UK studies: **Indices of Multiple Deprivation (IMD)**	As reported
Medical history	
Smoking status	Non-smoker Yes, but stopped before conception Yes, current smoker (and how many cigarettes)

Alcohol intake	Alcohol intake before pregnancy and now
Folic acid supplementation	Yes/no
Substance use before pregnancy	Never Acid Aerosols Amphetamines Cannabis Cocaine Crack Crystal meth Diazepam Ecstasy Glue Heroin Ketamine Khat Lighter fuel Methadone Speed Subutex Temazepam Other
Blood pressure: **Systolic** **Diastolic**	Blood pressure at booking (mmHg)
Previous C-section	Yes/no
Previous macrosomia	Yes/no
Previous gestational diabetes (GDM)	Yes/no
Previous bariatric surgery	Yes/no
Previous pregnancy hypertension	Yes/no
Diabetes history	None Type 1 Type 2
Family history of diabetes	None Type 1 Type 2
Previous spontaneous preterm birth or mid trimester loss	Previous spontaneous preterm birth or mid trimester loss between 16+0 and 34+0 weeks gestation
Cervical trauma	Previous cone biopsy (cold knife or laser) Large loop excision of the transformation zone (LLETZ - any number) Radical diathermy Other None
Cervical length <25 mm	Yes/no
Family history of preeclampsia	Yes/no
Essential hypertension	Yes/no
Previous pregnancy hypertension	Yes/no
Chronic renal disease	Yes/no
Autoimmune disease	Yes/no
Last pregnancy >10 years ago	Yes/no
Previous low birth weight <10%	Yes/no
Previous still birth	Yes/no
Previous neonatal death within 4 weeks of life	Yes/no
Maternal adiposity measures	

Ultrasound scans (record gestational week as reported across studies):	
Subcutaneous abdominal fat (SAT)	Number (mm)
Visceral abdominal fat (VAT)	Number (mm)
Total abdominal fat (TAT) as a sum of SAT and VAT	Number (mm)
Subcutaneous pre-peritoneal fat	Number (mm)
Visceral pre-peritoneal fat	Number (mm)
Total pre-peritoneal fat	Number (mm)
Anthropometry (record gestational week as reported across studies):	
Waist circumference	Number (cm)
Hip circumference	Number (cm)
Height	Number (cm)
Weight	Number (kg)
Neck circumference	Number (cm)
Mid upper arm circumference	Number (cm)
Skinfold thicknesses (Biceps, Triceps, Subscapular, Iliac crest, Supraspinale)	Number (mm)
Body mass index (BMI)	weight(kg)/height^2 (m)
Waist to hip ratio	Waist circumference/Hip circumference
BMI and waist to height ratio	The combination of BMI and waist to height ratio (NICE 2025)
Waist to height ratio	Waist circumference/Height
Body Adiposity Index	Hip circumference (cm)/ Height (m)$^{1.5}$ -18 (x1000; derive numbers in the order of magnitude of Waist circumference)
A Body Shape Index (ABSI)	1000*Waist circumference*Weight$^{-2/3}$ *Height$^{5/6}$;
Hip Index	Hip circumference*Weight$^{-0.482}$*Height$^{0.310}$
Weight-Adjusted Waist Index	(Waist circumference *100)/(Weight$^{0.5}$)
Body Roundness Index	364.2-365.5*(1((0.5* Waist circumference/p)^2/(0.5*Height)^2
Abdominal Volume Index	(2*(Waist circumference *100)^2 + 0.7*(Waist circumference *100-Hip circumference*100)^2)/1000
Conicity Index	Waist circumference/(0.109*(Weight/Height)$^{0.5}$))
Estimated Total Body Fat	100*(-Z+A-B)/C A=(4.15* Waist circumference*39.3701),B=(0.082* Weight *2.20462),C=(Weight*2.20462) Z=98.42 (males); 76.76 (females)
Relative Fat Mass	64-(20* Height/Waist circumference)+(12*S) S= 0 (males); 1 (females)
Clínica Universitaria de Navarra Body Adiposity Estimator (CUN-BAE)	−44.988 + (0.503*age) + (10.689*S) + (3.172*BMI) − (0.026*BMI^2) + (0.181*BMI*S)− (0.02*BMI*age) − (0.005*BMI2*S) + (0.00021* BMI^2*age) S= 0 (males); 1 (females)
Measure of truncal fatness: Subscapular/Triceps ratio	Subscapular skinfold/triceps skinfold

3.2 Defining Populations for Analysis

The population for analysis will follow that specified in the SHAPES Cohort study (see section 2.1 in the SHAPES cohort SAP (SHAPES Cohort SAP 2025) for details) (Heslehurst et al. 2023).

4. OUTCOMES

4.1 Definition and Calculation of Harmonised Outcome Measures and Variables

Where applicable, full details about how outcomes have been calculated (as well as dealing with missing data and any recoding) for each harmonised outcome and variable are given below.

Table A in the Appendix in Section 6 of the SHAPES Cohort SAP (SHAPES Cohort 2025) describes outcome measures and variables to be used and these will be considered in the SHAPES-IPD MA. The outcomes in Table A are based on the SHAPES Cohort study and definitions/criteria may vary across collaborating studies providing IPD. If definitions are considerably different to the SHAPES Cohort, then sensitivity analyses may be conducted (see section 5.4).

5. IPD MA

5.1 Two stage approach

The SHAPES-IPD MA will be reported according to PRISMA-IPD guidelines (Stewart 2015). We will use the two-stage approach (Fisher 2015; Maxwell 2014; Tierney 2024). Stage 1 involves the collaborating study IPD being analysed separately for each study using a statistical method appropriate for the type of data being analysed (informed from the SHAPES Cohort analyses). This relates to attempting to externally validate the findings of the SHAPES Cohort risk prediction analysis in heterogeneous external populations as specified in the objectives in section 1.5. Regression analyses (in accordance with the modelling outlined in the SHAPES Cohort SAP in section 2.5 (SHAPES Cohort SAP 2025)) will be performed to obtain effect estimates in each study separately.

Stage 2 then combines effect estimates (β (i)) and variance using standard MA methods suitable for aggregate data (Riley 2023); however, rather than extracting aggregate data from published articles, the stage 1 results provide the aggregate data for stage 2. Aggregate data are then pooled using standard MA methods. This can be computed by inputting data using Generic Inverse Variance Method in Revman or using the Stata command ipdmetan for two-stage IPD meta-analysis of any measure of effect (Fisher 2015). This will be informed from the SHAPES Cohort analyses and is likely to be a measure of discrimination such as the C index or D statistic (Pencina 2019; Riley 2016; Steyerberg 2010). We will use the random effects model to capture heterogeneity between studies, and the estimation will be done using REML. The 95% confidence interval for the pooled effect will be derived as appropriate with consideration given to the Hartung-Knapp approach (Hartung 2001). Calibration and discrimination measures will be used to summarise the model's performance. If the C-statistic is reported, these will follow from work outlined in the SHAPES cohort study SAP (e.g. likely to be pooled on the logit scale, as this is a more appropriate scale for pooling C-statistics in a meta-analysis) (Snell 2017). The calibration slope and calibration-in-the large

will be pooled on their original scale. Interactions will not be included in the SHAPES cohort study, so will not be considered in the IPD MA. Imputation will not be performed for systematically missing variables across studies, but handling of missing variables and outcomes is described in section 5.2 below.

A two-stage approach was preferred to the one stage as it allows forest plots and heterogeneity statistics to be presented. With respect to heterogeneity, the I^2 statistic will be calculated; this statistic indicates the % total variation due to between-study variance (Deeks 2024). Additionally, the two-stage approach can easily incorporate both IPD and aggregate data estimates and so facilitate sensitivity analyses (see section 5.4 below). It is widely accepted in the literature that both the one and two-stage approaches give similar (if not identical) results most of the time (Riley 2023). Discrepancies can largely be explained by different assumptions rather than the number of stages (Fisher 2015). The two-stage approach is simple, allows standard meta-analysis methods to be used and can readily be implemented in packages like Stata using the *ipdmetan* command (Fisher 2015; Riley 2023).

5.2 Missing data

Each IPD will be assessed by the SHAPES-IPD study team for completeness and quality of data collected on the study database. We will consider the use of multiple imputation if primary outcome data (and associated predictor variables in the model) are considered missing to a sufficient extent (e.g. if >20% missing in each cohort, but no more than 50% is missing). MI will be considered within each included study, and data will not be considered from different or external studies. Similar consideration may be made for secondary outcome measures. In the event of using imputation, we will plan to use multivariate imputation by chained equations (MICE)(White 2011) or follow any precedent set in the SHAPES Cohort study SAP (SHAPES Cohort SAP 2025). We will also consider imputation for covariates included in regression models. We will not impute covariates not collected in a study.

5.3 Subgroup Analysis

Subgroup analyses will be performed grouping studies by countries closely aligned to a UK healthcare setting. If enough studies are identified this may be restricted to UK studies only, but more likely this will be by context (e.g. similar European countries and high-income countries globally) or by continent.

Subgroup analyses will also be performed within different ethnic groups. The rationale for this relates to the evidence-base that some ethnic groups have higher adiposity-related risk at lower BMI and waist circumference cut points than white populations (Iliodromiti 2022). This may also be applicable for other individual measures of adiposity. For the risk prediction models, ethnic group may be an existing covariate, removing the need to conduct sub-group analysis. Sub-group analyses will be conducted in risk prediction models, where ethnic group is not a covariate.

Gestational age is likely to be mixed across studies and not as narrow as the 11 weeks 2 days to-14 weeks and one day inclusion in SHAPES. Therefore, we will additionally perform subgroups by gestational age in the study (grouping by 11-14 weeks, 15-17 weeks, 18-20 weeks or by a suitable mean cut off as appropriate). Studies were excluded if they reported adiposity measurements taken after 20 weeks (and no earlier).

If BMI is not included in the final model, we will perform a subgroup analysis splitting by a BMI of below or above 35 to see if it works differently in those populations. We may explore further post hoc sub-group analyses of interactions with BMI and other individual adiposity measurements if appropriate. The completion of these subgroups will depend on whether BMI is included in the final risk prediction model.

5.4 Sensitivity Analyses

We may perform sensitivity analyses if primary outcome data (e.g. GDM) are considered missing to a sufficient extent and compare with the full case analyses (e.g. if >20% missing in each cohort, but no more than 50% is missing). MI will be considered within each included study, and data will not be considered from different or external studies. Similar consideration may be made for secondary outcome measures. In the event of using multiple imputation, details are outlined in section 5.2 above. We will not impute any outcomes or covariates with missing data that are below this missing threshold (No more than >20% missing). Datasets in studies that have variables that are sought but were not reported will not be imputed or included in the IPD MA.

SA will apply to the primary outcome (GDM) in the first instance, and we will additionally consider important secondary outcomes should conclusions differ with regards to the primary outcome.

An IPD-only meta-analysis may be biased if unavailability of IPD is related to the study results (Riley 2007). Therefore, we may conduct SA combining IPD and aggregate data studies in the same MA. Such aggregate data studies can easily be included in step 2 of a two-stage IPD MA. At present, we have identified six such studies, and these will be incorporated in sensitivity analyses to test the robustness of the results. If the non-IPD studies do not adjust for the same variables sought in the IPD modelling, they will be excluded from the analyses. The addition of aggregate data studies in the MA is likely to increase the observed heterogeneity so we will report the I^2 values too as outlined in section 5.1 above. A sensitivity analysis will be conducted including only studies that closely match the gestational ages specified in the SHAPES cohort study (Heslehurst et al. 2023).

We will additionally conduct SAs by definition of GDM. The core analysis will use GDM diagnosis as reported by each study regardless of the diagnostic criteria that were used. If possible, we will repeat the analyses using different GDM definitions based on diagnostic criteria. Where possible, we will attempt to standardise the definition of GMD using SHAPES criteria. This is defined by NICE as fasting plasma glucose level of ≥ 5.6 mmol/litre or 2-hour plasma glucose level of ≥7.8 mmol/litre. If this is not possible, then our alternative option will be to use the IADPSG or WHO criteria. The IADPSG criteria is defined as at least one maternal plasma glucose concentration should be equal to or above the upper limit—set at 5.1 mmol/L for fasting measurements, 10 mmol/L for 1-hour measurements, and 8.5 mmol/L for 2-hour measurements—for GDM to be diagnosed. The WHO have subsequently adopted these criteria.

5.5 Statistical Software

Analyses will be carried out using appropriate statistical software packages including Stata (Stata 2023. *Stata Statistical Software: Release 18*. College Station, TX: StataCorp LLC) and RevMan (Review Manager (RevMan). Version 5.4. The Cochrane Collaboration, (released

May 2020). R (R Core Team 2025) may additionally be used for stage 1 analyses so that the code used for modelling work in the cohort study can be utilised. Software versions will be recorded at the time of analysis.

6. STORAGE AND ARCHIVING

The SHAPES Chief Investigator has overarching responsibility for collection, quality, and retention of data. All data will be obtained anonymised from collaborators and securely transferred using methods agreed with each collaborating study team. All data will be held on secure university servers that only specified members of the SHAPES study team have access to (the CI, research associate and statistics team). The server is NHS approved for patient data storage with the highest level of data security. Data will be accessed following the Newcastle University Data Security Protection Toolkit Information Security Policy.

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8. APPENDIX

Appendix 1: PRISMA Flow chart showing process of study selection, at the time of the SAP sign off