Title: External validation of maternal obesity risk prediction models: the international Study of How Adiposity in Pregnancy has an Effect on outcomeS Individual Participant Data (SHAPES-IPD) meta-analysis protocol

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Abstract

Introduction: Maternal obesity studies show that populations with a BMI≥30kg/m^2 have increased risk for pregnancy complications. Guidelines use BMI to triage obesity care; however, BMI poorly predicts individuals' obesity-related risk compared with adiposity measures. Risk prediction research can identify sensitivity and specificity of adiposity measures to better target obesity care. Clinical risk prediction models require validation in external populations before implementation. This study aims to validate existing maternal adiposity risk prediction models

(developed using the UK SHAPES Cohort), using international individual participant data (IPD) meta-analysis as external validation datasets.

Methods and analysis: IPD has been shared for this study. Searches to identify IPD included six electronic databases, grey literature sources, citation chaining and contacting authors (February 2021 to July 2022). Searches identified 93 published and unpublished sources of maternal adiposity and pregnancy outcome data. Authors were invited to join the SHAPES-IPD Collaborative Group, resulting in 20 shared IPD datasets (n=15 countries, n=15,568 pregnancies). All IPD cohort studies will be quality assessed using Newcastle-Ottawa Cohort Study scale. A 2-stage IPD meta-analysis will be conducted and reported according to PRISMA-IPD guidelines. Stage-1 will involve regression analyses to replicate and assess existing model(s) performance in new populations by examining calibration and discrimination statistics. We will obtain these estimates (e.g. c-index, D statistic) for each study, reducing the IPD to aggregate study-level data. Stage-2 will combine these aggregate data using standard meta-analysis methods and random effects models. Heterogeneity will be assessed by visual inspection of forest plots and by calculating the I^2 statistic.

Ethics and dissemination: Newcastle University Faculty of Medical Sciences ethics committee approved this research (REF. 2787/47918, date 02 July 2024). All included studies have their own ethics approval. Results will be published in peer-reviewed journals, as well as informing health economics analysis and future guideline recommendations.

Registration: PROSPERO 2022 CRD42022310760.

Keywords: Maternal obesity; risk prediction adiposity; pregnancy; individual participant data; meta-analysis

Strengths and limitations of this study – max 5 bullet points

- The use of individual participant data (IPD) meta-analysis provides greater statistical power than traditional aggregate data approaches, allows for harmonisation of key variables and standardisation of analysis methods, enabling more precise evaluation of how maternal adiposity measurements predict adverse pregnancy outcomes.
- External validation of UK-developed maternal adiposity risk prediction models across diverse international datasets will enhance confidence in the reliability and generalisability, and their potential utility in informing clinical decision-making and healthcare policy.
- IPD meta-analysis methodology should reduce the risk of common biases such as publication bias, selection bias, and confounding, which often affect traditional meta-analyses or single-cohort studies.
- Limitations include incomplete access to relevant international datasets and the presence of missing data within included cohorts, which may affect model validation and generalisability.

- Only 22% of the eligible studies identified have provided data to be included in the IPD meta-analysis, which may introduce selection bias and limit the representativeness and generalisability of the validation findings.

Introduction

Observational population studies explore patterns in the associations between risk factors and health outcomes. Population studies exploring maternal obesity, when defined using body mass index (BMI) ≥30kg/m^2, show significant positive associations with multiple adverse pregnancy outcomes. These include gestational diabetes (GDM), preeclampsia, congenital anomalies, maternal and perinatal mortality, large-for or small-for gestational age (LGA/SGA), pre- and post-term birth, instrumental and caesarean delivery, maternal infection, and postpartum haemorrhage. [1-4] These multiple increased risks have informed the development of clinical guidelines which use maternal BMI to triage high-risk care including additional referrals, screening, and closer monitoring. [5 6] However, an international study showed that approximately half of women with obesity, according to BMI, have uncomplicated pregnancies, and approximately 40% of women with a BMI in the overweight range do develop complications usually associated with obesity [7]. These patterns raise questions about the utility of BMI to accurately predict obesity-related risk during pregnancy.

Currently, pregnancy guidelines in the UK and internationally only use BMI to identify pregnant individuals that have increased obesity-related risk and inform care plans. [5 8-10] Although BMI is a good indicator of population-level trends in health, it can be a poor indicator of individual-level risk as it does not account for adipose tissue amount and distribution. Alternative measures of body fat distribution (e.g. waist circumference, waist to height ratio), type (e.g. visceral or subcutaneous), and amount (e.g. volume or thickness) have been shown to better identify individual-level risk in non-pregnant populations. [11-13] Clinical guidelines for non-pregnant populations have incorporated additional adiposity measures (such as waist circumference and waist to height ratio) alongside BMI to identify individuals who have increased obesity-related risk; [14 15] however, these do not yet exist for pregnancy.

Two systematic reviews have been recently published exploring associations between measures of adiposity in pregnancy and maternal and infant health outcomes. [16 17] These reviews identified multiple candidate adiposity measures (including waist circumference, waist to hip ratio, neck circumference, visceral fat, skinfolds and fat free mass) that were significantly associated with an increased risk of a range of maternal and infant health outcomes (including GDM, pregnancy induced hypertension, preeclampsia, delivery complications, birthweight, macrosomia, SGA, preterm delivery, neonatal morbidity and mortality). However, there is a lack of evidence directly comparing the use of candidate adiposity measures with BMI for individual risk prediction in pregnancy.

Improving risk prediction would inform targeted and more cost-effective obesity care in pregnancy. Risk prediction research requires the development and validation of risk prediction models before any implementation into routine healthcare services. [18] The SHAPES research programme (https://research.ncl.ac.uk/shapes/) aims to identify measures of adiposity which may predict risk of a range of obesity-related adverse pregnancy outcomes more accurately than

current use of BMI. The research programme consists of three stages: 1) risk prediction development using a prospective cohort study in the UK – the SHAPES Cohort; [19] 2) risk prediction external validation using IPD from heterogeneous international populations and 2-stage meta-analysis methods; and 3) exploration of the cost-effectiveness of an alternative method of risk prediction compared with using BMI alone. This protocol describes stage 2 of the research programme. The aim of this study is to externally validate the performance of the SHAPES Cohort risk prediction models (stage 1) in heterogeneous populations using IPD meta-analysis methods.

Methods and analysis

This research will be undertaken and reported using recommendations on risk prediction validation and IPD meta-analysis methods and reporting guidelines. [20-23] The protocol was registered on the international prospective register of systematic reviews (PROSPERO 2022 CRD42022310760).

Literature search

The identification of eligible datasets for the SHAPES-IPD study builds on two published systematic reviews reporting associations between early pregnancy adiposity measures and adverse maternal and infant pregnancy outcomes. [16 17] The search strategies are reported in full in the published papers. In brief, they involved searching MEDLINE, EMBASE, PsycINFO, CINAHL (EBSCO), JBI Database of Systematic Reviews and Implementation Reports and Cochrane Library using search terms related to the following concepts: "Pregnancy", "Adiposity", "Prediction/Risk" and "Outcomes". "Outcomes" included generic vocabulary to capture all possible pregnancy outcomes. Language restrictions were not applied to the electronic searches. Electronic databases were searched from inception to April 2021 and were supplemented by forwards and backwards citation chaining and contacting authors to confirm data availability and study eligibility (completed July 2022). The included cohort studies from both reviews were screened against the SHAPES-IPD inclusion criteria. The studies excluded from both original systematic reviews were also re-screened to identify any cohorts that had the required adiposity and pregnancy outcome data for IPD analysis but had been excluded from the previous reviews because associations were not reported. Forwards and backwards citation chaining was completed for all included studies.

Additional searches were conducted from February 2022 up to July 2022 to identify any unpublished data sources with the required variables for the SHAPES-IPD study that had not been identified in the previous searches. We used relevant national information sources to search for potential unpublished data sources (www.birthcohorts.net, the Medical Research Council cohort directory, and the International Journal of Epidemiology cohort profiles). Details of the search terms are in Appendix 1. Study authors were contacted by email and using social media

and invited to collaborate in the SHAPES-IPD study from August 2022, with the deadline to obtain the IPD being end of January 2025 (total duration of 30 months).

Eligibility criteria

Inclusion and exclusion criteria used the PECOS framework. [24] The population (P) were pregnant women with singleton pregnancies. Datasets that also had included multiple pregnancies in addition to singletons were included as the appropriate inclusion criteria could be applied to the IPD before analysis. We excluded any studies reporting restricted populations of pregnant women with underlying conditions (e.g. only including women with type 2 diabetes). The exposure (E) was early pregnancy measures of adiposity (e.g. weight, height, waist circumference, hip circumference, mid-arm circumference, neck circumference, skinfold thickness, visceral fat, subcutaneous fat) measured before 20 weeks' gestation. Studies that only reported BMI and no other adiposity measure, or only pre-pregnancy or postnatal adiposity measures, were excluded. Studies exploring low adiposity/under nutrition were excluded as the focus of SHAPES is on obesity-related risk. No inclusion or exclusion criteria were applied for the comparison group (C) as the IPD would standardise this across studies. Any pregnancy outcomes (O) included in the SHAPES Cohort study were included. [19] GDM is the primary outcome of interest, and additional outcomes include gestational hypertension, pre-eclampsia, modes of delivery (induction of labour, Caesarean section, instrumental delivery), retained placenta, maternal infection, blood loss during pregnancy, pre- and late-term birth, large for gestational age, small for gestational age, neonatal respiratory distress, feeding method (first feed and feed method at discharge, infant admission to specialist care). Studies needed to include variables for at least one adiposity exposure and one pregnancy outcome. Studies reporting maternal adiposity, and first trimester miscarriage were excluded as SHAPES Cohort participants were not eligible if they had a miscarriage at the time of the dating scan appointment (approximately 12 weeks' gestation). Eligible study designs (S) were prospective or retrospective cohort studies. Nested case control studies were included if the source data from the full cohort could be requested for the IPD. Trial cohorts were excluded due to the potential for intervention effect. We did not restrict by country of study.

Study selection, IPD collection and harmonisation

Endnote (version 21)[25] was used for reference management. The results of the literature searches were screened in duplicate against the eligibility criteria using Rayyan. [26] The searches identified 93 studies with data on at least one adiposity measure and one pregnancy outcome of interest (Appendix 2). Study level data will be extracted related to methods, sample size, population characteristics, and any risk prediction results reported.

Authors were contacted and invited to be part of the SHAPES-IPD collaboration between August 2022 and December 2024. Corresponding authors were contacted by email, and if there was no response the contact details for co-authors were sought and invitations sent to the wider research team. We sent up to five follow up emails to authors of eligible studies. If we received no response by email, or encountered non-functional email addresses, we attempted to contact authors through their institutions, social media and online research accounts (LinkedIn, Twitter, ResearchGate, ORCID). It was not possible to contact authors of two studies as we could not identify current contact details (2.2%). We did not receive any response from authors of 51 studies (54.8%) following five email attempts and additional contact methods (Supplement 2). We received responses from authors of 40 studies (43.0%); of these, 10 (10.8%) authors declined the invitation due to no longer having access to the dataset or a lack of interest or capacity to collaborate, and 30 (32.3%) authors agreed to join the SHAPES collaboration. Final follow up emails to authors who had expressed an interest in collaborating were sent in December 2024 and nine (9.7%) studies were excluded: seven due to non-responsiveness to communications, one due to UK Government enforced data sharing restrictions, and one study required an ethics resubmission which would not be completed in the SHAPES-IPD analysis timeline (see Appendix 2). The IPD was shared for analysis by 19 authors for 20 studies (21.5%) comprising of 15,568 pregnancies. The IPD for one additional dataset could not be shared directly due to data transfer restrictions (GDM cohort, n=22,302 pregnancies); [27] however, the authors agreed to replicate the SHAPES-IPD statistical analysis plan (SAP) for stage 1 of the IPD meta-analysis and share their aggregate data for inclusion in the stage 2 meta-analysis. The results of this study may be included if they are provided before the meta-analysis is finalised. Authors representing each study were invited to join the SHAPES-IPD Collaborative Group (https://research.ncl.ac.uk/shapes/informationforresearchers/2individualpatientdataipdmeta-analysis/). To date, the SHAPES-IPD collaboration includes 20 researchers from 21 studies in 15 countries (Table 1).

Table 1: Characteristics of the included IPD studies and datasets

Author year: Cohort name (if available)	**Country**	**Study time**	**Sample size**[$]
Backstrand 1995 [28]	Mexico	1984- 1986	76
Bai et al. 2020 [29]	Australia	2018- 2019	117
Jarvie et al. 2020 [30]	Scotland, UK	2010- 2011	45
Guillemette et al. 2015: [31] Genetics of Glucose regulation in Gestation and Growth (Gen3G) study	Canada	2010- 2013	878
Lopez et al. 2011 [32]	Argentina	2005- 2006	1554
Vieira et al. 2017: [33] SCOPE consortium	Ireland*	2004- 2011	1774

Wibowo et al. 2020 [34]	Indonesia	2017	134
Sommer et al. 2015: [35] the STORK Groruddalen study	Norway	2008- 2010	823
Rocha et al. 2020 [36]	Brazil	2016- 2017	133
Bernardi et al. 2021 [37]	Brazil	2017	270
Redfern et al. 2021 [38]	UK	2015- 2016	75
Subhan et al. 2019 [39]	Canada	2009- 2012	1820
Sarac et al. 2019: [40] Croatian Islands' Birth Cohort Study	Croatia	2016- 2018	500
Inskip et al. 2005: [41] Southampton Women's Survey	UK	1998- 2007	2600
Steegers-Theunissen et al. 2016: [42] The Rotterdam Periconceptional Cohort (Predict)	Netherland	2010- 2015	792
Piuri et al. 2017 [43]	Italy	2012- 2014	126
Taebi et al. 2015 [44]	Iran	2008- 2010	1000
Diaz et al. 2020: [45] GLOWING study	USA	2011- 2014	209
Poustchi et al. 2018: [46] The Prospective Epidemiological Research Studies in Iran Birth Cohort (the PERSIAN Cohort Study)	Iran	2016- 2018	2000
Han et al. 2017: [27] Tianjin GDM cohort	China	2010- 2012	22,302
Sattar et al. 2001: [47]GOAL study	UK	1997- 1999	1142

*Note: *Additional data from SCOPE exists for Australia, New Zealand and the UK (SCOPE total n=5592) – at the time of publication only Ireland data had been shared.*
[$] sample size: The sample size used for SHAPES IPD study

The process of obtaining the IPD was facilitated by the research funding and the cooperation of study personnel. A PRISMA IPD flow chart [23] was used to record the flow of results throughout the screening and selection process, and the reasons for exclusions, in the final reporting (Figure 1).

A data protection impact assessment was conducted at Newcastle University to identify data sharing risks and management plans. Data sharing agreements were established between Newcastle University and the collaborating organisations. Anonymised/de-identified data from collaborators are stored on a secure data repository at Newcastle University, with restricted access to members of the Newcastle University research team who require access for data cleaning, harmonisation, coding, analysis and reporting.

Details of the harmonisation and mapping process is given in the statistical analysis plan (SAP). [48] In summary, the IPD obtained from eligible studies will be compared with the data extracted from their published papers (if available). Data will be cleaned, any missing data, errors, inconsistencies between variables or outlying values will be queried and rectified through input from the original authors. Variables from eligible studies will be harmonised with other included IPD datasets.

Quality and risk of bias assessment

Quality and risk of bias assessments will be carried out using the Newcastle-Ottawa Scales for cohort studies to assess information bias, selection bias, and confounding. [49] Any risk prediction studies will be assessed using the PROBAST (Prediction model Risk of Bias Assessment Tool): a tool to assess risk of bias and applicability of prediction model studies following four domains: participants; predictors; outcome; analysis. [50] Overall risk of bias and applicability judgements will be carried out for each study by two independent review authors. Disagreements will be resolved through discussion in the first instance, and recourse to independent review by a third author if required.

Heterogeneity

Key sources of heterogeneity include differences in demographic variables that have been used in the included studies, especially those that may differ to the SHAPES Cohort variable definitions such as UK ethnic group categories and the index of multiple deprivation (IMD) to estimate socio-economic status. Difference in variable definitions can impact prognosis and test performance. Full details of subgroup and sensitivity analyses are outlined in the SAP. We will assess heterogeneity through visual inspection of forest plots and by reporting the I^2 value. Further details are provided in the SAP. [48]

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 considerations may be made for secondary outcome measures. In the event of using imputation, we will plan to use multivariate imputation by chained equations (MICE)[51] or follow any precedent set in the SHAPES Cohort study SAP. [52] We will use imputed datasets and follow any precedent set in the SHAPES Cohort study SAP. [52] We will also

consider imputation for covariates included in regression models. We will not impute covariates not collected in a study.

Statistical analysis

A SAP has been developed to outline the IPD meta-analysis. [48] This includes full details of the methods, including the harmonisation process, covariates and outcomes, IPD meta-analysis methodology, handling missing data, subgroup and sensitivity analyses and details of statistical software. The IPD meta-analysis will be reported according to PRISMA-IPD guidelines. [23] A flow diagram will be drawn up showing the number of studies identified through to the number of studies and participants included in the analysis.

In summary, we will conduct a two-stage meta-analysis. In the first stage, the prediction model developed using the SHAPES cohort data will be applied to each participant from each participating IPD study to obtain their predicted outcome probability (for binary outcomes).

These predicted probabilities will be compared to those observed in order to estimate the model's predictive performance statistics such as calibration slope, calibration-in-the-large, C statistics/AUROC (following the models identified in the SHAPES cohort study). The IPD will be analysed separately, and the results pooled with results from other IPD in the meta-analysis. In the second stage, the effect estimates obtained from each of the different model performance statistics across participating IPD studies will be combined, using a standard meta-analytic approach. [53] 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. [54] 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 [52](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). [55] The calibration slope and calibration-in-the large will be pooled on their original scale. Imputation will not be performed for systematically missing variables across studies, but handling of missing variables and outcomes is described above.

The studies that were identified by the searches that have not provided IPD will be reviewed to identify any aggregate data reported that could be included in stage 2 of the meta-analysis. At present, we have identified six such studies, and these will be incorporated in sensitivity analyses to test the robustness of the results. Other subgroup and sensitivity analyses are also specified in the SAP. [48] This will include the combination of BMI (<35 kg/m² and BMI ≥35 kg/m²) and waist to hip ratio which was included in NICE guidance in non-pregnant populations. [14]

Ethics and dissemination

Favourable ethical opinion was given by Newcastle University Faculty of Medical Sciences ethics committee (REF. 2787/47918, date 02 July 2024). All data will be obtained anonymised/

de-identified 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 Chief Investigator (NH), SHAPES Research Associate (GN), and statistical team (DT, AB, MS)). The server is NHS approved for patient data storage with the highest level of data security. Data will be accessed following Newcastle University Data Security Protection Toolkit Information Security Policy. Results of this study will be published in peer-reviewed journals. 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.

Research collaboration communication

Communication with the SHAPES-IPD Collaborative Group uses email, video calling and the SHAPES website for updates and collaborative working. A 2-day collaborators hybrid meeting was held at Newcastle University (April 2025) to discuss the IPD data, harmonisation, SAP, study protocol and co-authorship agreements.

Reporting data

In the final report we will clearly present the methods of the review and included study data, such as tabulated characteristics of included studies and details of study designs. The report will conform to recommendations in the PRISMA-IPD checklist (see Appendix 3). Formal synthesis of the results and assessments of study quality and risk of bias will also be presented in full.

Discussion

The SHAPES research programme, including a Cohort study (risk prediction model development), IPD meta-analysis (external validation study), and health economics analysis (informed by both the Cohort study and IPD meta-analysis) will help to address current evidence gaps and inform evidence-based decision making. Our systematic searches for evidence have identified many studies that explore associations between maternal adiposity and pregnancy outcomes. However, there are limited studies focusing explicitly on individual risk prediction to inform targeted care. Similarly, there are a lack of studies to date that explore a wide range of different adiposity measures and pregnancy outcomes to facilitate direct comparisons of the performance in the same population, and with current practice using BMI. The SHAPES Cohort study addresses these research gaps to provide evidence on the optimal adiposity measures, and risk prediction models, for a range of pregnancy outcomes.

External validation is critical before implementing prediction models in clinical practice. This requires datasets separate from those used for model development, which IPD meta-analyses facilitate through methods like internal-external cross-validation. Aggregate data meta-analyses are typically limited to summary statistics, such as population mean values, which hinders the evaluation of multiple predictors or the synthesis of evidence across studies. In contrast, IPD meta-analyses leverage individual-level data to enable larger sample sizes, facilitate the assessment of multiple prognostic factors, and recalibrate prediction models for more precise individual risk predictions. The SHAPES-IPD approach can facilitate validation of risk prediction models across cohorts, ensuring robust and generalisable findings. The ability to evaluate model performance across diverse studies enhances confidence in clinical applicability.

There are some challenges to harmonisation of data across diverse international contexts, particularly relating to socio-demographic data. For example, ethnic group differences in populations results in different variable categories between studies that need to be consistently defined across datasets. There are also differences in the methods used to define socio-economic status between countries. While some of these challenges may be impossible to overcome, acknowledging and addressing variations between contexts is critical for ensuring models are sensitive to diverse population contexts.

A robust prediction model must deliver accurate, consistent performance, be validated across clinical settings and subgroups, and support improved clinical outcomes by informing decisions acceptable to patients and clinicians. By addressing these challenges, SHAPES leverages IPD meta-analyses to develop and validate robust, clinically relevant prediction models for adverse pregnancy outcomes. The results of the entire SHAPES research programme, including the health economics analysis and a parallel qualitative study with SHAPES Cohort participants on experiences of adiposity measurements, will help policy makers and care providers to make evidence-based decisions on the most effective and acceptable measures for wide-scale implementation into routine care. This should ultimately improve care and outcomes for pregnant individuals and their babies.

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Appendices

Appendix 1

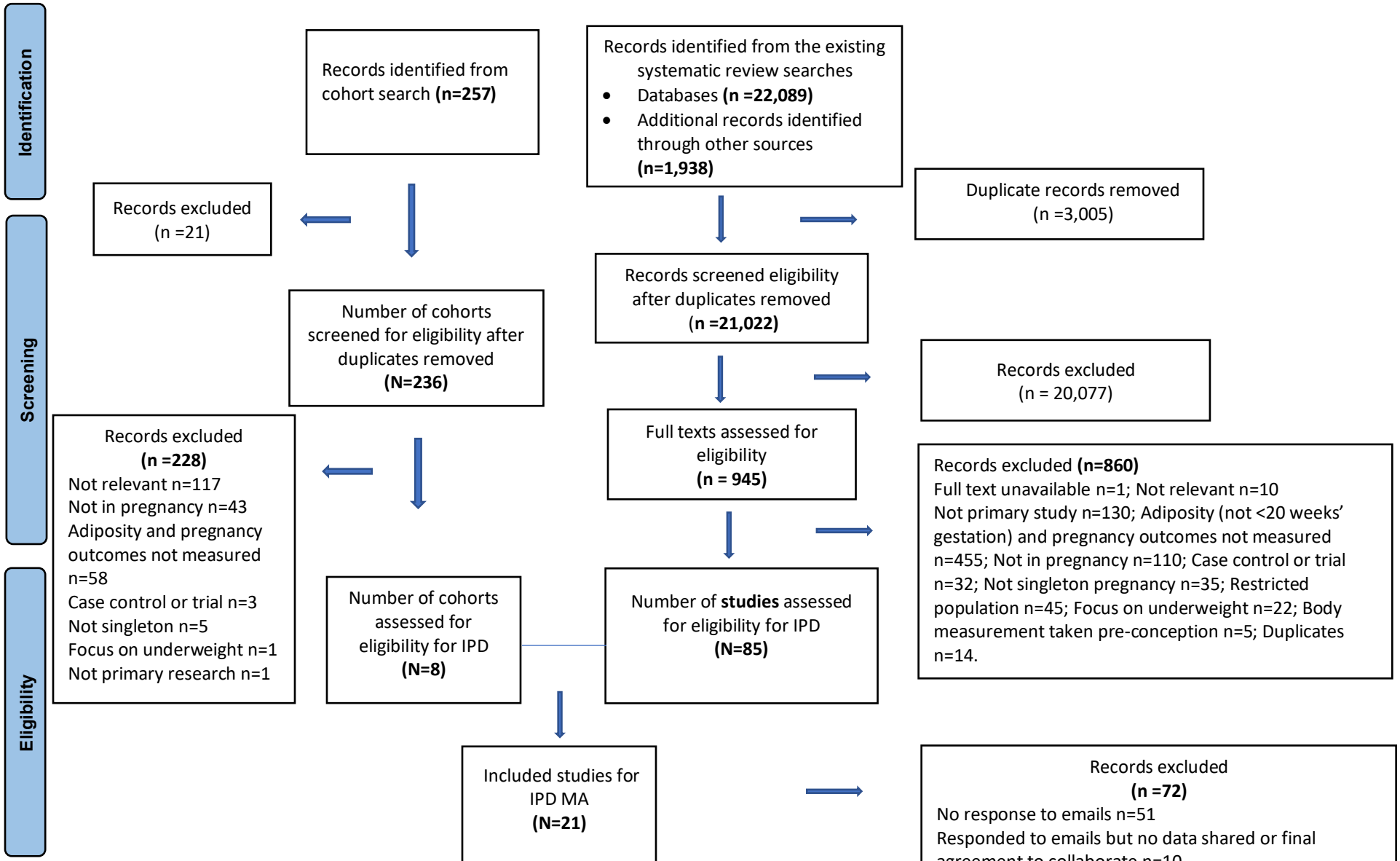
Cohort search strategy

Source	Date completed	URL/search terms	Number screened
Snowball (relevant refs cited in any of the above)	Jul-19		33
http://www.birthcohorts.net/	Jul-19	1) Mothers > Maternal health > WC 2) Mothers > Maternal health > Bioimpedance 3) Mothers > Maternal health > Metabolism 2) Mothers > Maternal health > DEXA scan	16
MRC Cohort Directory (UK)	Jul-19	I searched 2 ways: Keyword search for 'pregnancy'; Drilled down by 'Female', Age 10-59 (to include reproductive age only). Then I ticked WC and HC.	18
International Journal of Epidemiology	Jul-19	Searched for: Section: cohort profiles; Topic: pregnancy. Note that 'topic' is not searchable, but all cohort profiles on the topic of preg can be selected by clicking on one (e.g. Shanghai Birth Cohort) and then selecting 'pregnancy'). Searching the Abstracts for 'pregnancy' doesn't work because they don't all have abstracts. Using Advanced Search using keyword doesn't work.	191
		Total identified:	**257**
		Duplicates	**21**
		1st screen	**236**
		Excluded	**220**
		2nd screen after contacting authors	**16**
		Excluded	**8**
		Eligibility	**8**

Exclusion table for Cohort search

IPD: Reason for excluding	**Numbers**
1 Full text unavailable	0
2 Not primary research	1
3 Not a quantitative study	0
4 Adiposity (< 20 weeks' gestation) and pregnancy outcomes not both measured	58
5 Not in pregnancy	43
6 Study design: case control or trial	3
7 Not singleton pregnancy	5
8 Restricted population	0
9 Focus on LBW/underweight/undernutrition	1
10 Not relevant (would not have made it to full text screening)	117
11 Duplicated within this cohort search or study search	21
Total	257

Appendix 2


Identification
Screening
Eligibility
Records identified from cohort search (n=257)
Records identified from the existing systematic review searches
Databases (n =22,089)
Additional records identified through other sources (n=1,938)
Records excluded (n =21)
Duplicate records removed (n =3,005)
Number of cohorts screened for eligibility after duplicates removed (N=236)
Records screened eligibility after duplicates removed (n =21,022)
Records excluded (n = 20,077)
Records excluded (n =228)
Not relevant n=117
Not in pregnancy n=43
Adiposity and pregnancy outcomes not measured n=58
Case control or trial n=3
Not singleton n=5
Focus on underweight n=1
Not primary research n=1
Full texts assessed for eligibility (n = 945)
Records excluded (n=860)
Full text unavailable n=1; Not relevant n=10
Not primary study n=130; Adiposity (not <20 weeks' gestation) and pregnancy outcomes not measured n=455; Not in pregnancy n=110; Case control or trial n=32; Not singleton pregnancy n=35; Restricted population n=45; Focus on underweight n=22; Body measurement taken pre-conception n=5; Duplicates n=14.
Number of cohorts assessed for eligibility for IPD (N=8)
Number of studies assessed for eligibility for IPD (N=85)
Included studies for IPD MA (N=21)
Records excluded (n =72)
No response to emails n=51
Responded to emails but no data shared or final agreement to collaborate n=10
Initially agreed to join the collaboration but no data shared or final agreement to collaborate n=9
Contact details not valid n=2

Appendix 3

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Where reported
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Yes
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	PROSPERO 2022 CRD42022310760)
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Yes
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes in Supp 1
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes

Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a yet for risk prediction reviews but we will give quality assessment and risk of bias and strength of evidence strong consideration.

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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