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Differential effects of diet and physical activity interventions in pregnancy to prevent gestational diabetes mellitus and reduce gestational weight gain by level of maternal adiposity: a protocol for an individual patient data (IPD) meta-analysis of randomised controlled trials

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ABSTRACT

Introduction Women and their infants are at increased risk of complications if gestational diabetes mellitus (GDM) or excessive gestational weight gain (GWG) occurs in pregnancy. Weight management interventions in pregnancy, consisting of diet and physical activity components are targeted based on maternal body mass index (BMI). However, the relative effectiveness of interventions targeted based on alternative measures of adiposity to BMI is unclear. This individual patient data (IPD) meta-analysis aims to explore whether interventions are more effective at preventing GDM and reducing GWG in women according to their level of adiposity.

Methods The International Weight Management in Pregnancy Collaborative Network has a living database of IPD from randomised trials of diet and/or physical activity interventions in pregnancy. This IPD meta-analysis will use IPD from trials identified from systematic literature searches up until March 2021, where maternal adiposity measures (eg, waist circumference) were collected prior to 20 weeks' gestation. A two-stage random effects IPD meta-analysis approach will be taken for each outcome (GDM and GWG) to understand the effect of early pregnancy adiposity measures on the effect of weight management interventions for GDM prevention and GWG reduction. Summary intervention effects with 95% CIs) will be derived along with treatment covariate interactions. Between-study heterogeneity will be summarised by I^2 and tau^2 statistics. Potential sources of bias will be evaluated, and the nature of any missing data will be explored and appropriate imputation methods adopted.

Ethics and dissemination Ethics approval is not required. The study is registered on the International Prospective Register of Systematic Reviews (CRD42021282036). Results will be submitted to peer-reviewed journals.

PROSPERO registration number CRD42021282036.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This individual patient data (IPD) meta-analysis builds on an established collaboration's (International Weight Management in Pregnancy) work and may provide new insights by exploring adiposity measures alternative to body mass index (BMI) in the context of targeting weight management interventions in pregnancy.
⇒ IPD provides increased power compared with aggregate meta-analysis and an opportunity to explore the potential benefit of targeting weight management interventions in pregnancy on alternative measures of adiposity, to BMI.
⇒ Potential limitations include missing data within the data set and heterogeneity of how adiposity measures were recorded.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as 'any glucose intolerance with the onset or first recognition during pregnancy' and occurs in approximately 2%–25% of pregnancies worldwide, depending on location.[1–3] In the UK, guidelines recommend risk factor-based screening for GDM at 24–28 weeks' gestation; risk factors include a body mass index (BMI) ≥30 kg/m^2 or a familial history of diabetes mellitus, however, women with previous GDM are offered an additional screening test as soon after their initial booking appointment as possible (10 weeks' gestation).[4] A major issue surrounding GDM is that there are no international guidelines for the screening and diagnosis of women for

GDM, for example, Australian, Canadian and American guidelines recommend screening of all women, with each of these countries using different screening strategies and cut-offs to diagnose GDM.[5]

GDM presents immediate risks to maternal health including increased likelihood of pre-term labour and developing hypertensive disorders of pregnancy, and in the infant a higher risk such as being born large for gestational age and shoulder dystocia.[6–8] Long-term impacts include increased risk of developing type 2 diabetes mellitus (T2DM) in later life for the mother, and infants exposed to GDM in-utero are more likely to develop obesity.[9 10]

Gestational weight gain (GWG) is essential to support pregnancy, the National Academy of Medicine (NAM) published guidelines for a maximum GWG per week, dependent on the women's preconception BMI.[11 12]However, data suggests that GWG recommendations are frequently exceeded; a recent meta-analysis of 1,309,136 women reported that excessive GWG occured in 47% of pregnancies, with subgroup analysis showing that this increased to 57% of pregnancies if women had obesity.[13] Excessive GWG is associated with increased risk of caesarean section, pre-eclampsia in mothers and high adiposity in childhood for infants.[14–17] An individual patient data (IPD) meta-analysis of observational data from 162,129 mothers and their children has shown that excessive GWG was associated with increased odds of childhood overweight/obesity for children aged 2–5 years; OR 1.39 (95% CI 1.30 to 1.49), 5–10 years; OR 1.55 (95% CI 1.49 to 1.60) and 10–18 years; OR 1.72 (95% CI 1.56 to 1.91).[18]

Due to the substantially increased risks of adverse pregnancy outcomes associated with maternal obesity, several high-income countries have published guidelines around enhanced care including GDM screening, additional monitoring of fetal growth, referral to a dietitian, pre-eclampsia monitoring and weight management interventions consisting of diet and/or physical activity components.[19–23] The need for robust and clear guidelines relating to GWG and weight management across preconception, pregnancy and post partum has been highlighted by a systematic review of 22 practice guidelines reporting that 45% were low quality with high variability between guidelines.[24]

BMI has utility in predicting population trends in weight status over time, however, BMI has been shown to be a poor predictor of both adiposity levels and individual risk relating to obesity in non-pregnant populations.[25] BMI is unable to provide information on distribution of adiposity which is important for disease risk, as increased central adiposity is associated with metabolic dysfunction, whereas subcutaneous adiposity does not have the same deleterious metabolic effects.[26] It is estimated that the diagnostic performance of BMI in non-pregnant populations for the detection of adiposity is 88% in women with overweight, and 49% in women with obesity, suggesting a poor correlation between BMI and adiposity.[27] For example, a systematic review and meta-analysis of 20 observational studies in patients with T2DM, showed that every kilogram (kg) of visceral adiposity was associated with a four-fold increased risk of T2DM in females (OR 4.24, 95% CI 1.64 to 11.02 p=0.003). Importantly, the degree of visceral fat mass cannot be captured by BMI alone, the authors concluded that reducing visceral fat mass and increasing fat-free mass should be a target for future interventions; through health-associated behaviours such as dietary practices and physical activity levels.[28] Therefore, adiposity may confer a benefit, compared with BMI, for understanding which women may develop GDM. Observational data from a multi-centre cohort, suggested that 47% of pregnant women with a BMI≥30 kg/m^2 had 'uncomplicated' pregnancies; defined as a normotensive pregnancy with delivery after 37 weeks', to a liveborn baby not deemed small for gestational age, with no other significant complications.[29] The same study identified that 42% of women with a BMI between 25 and 29.9 kg/m^2 did experience pregnancy complications.[29] This suggests that BMI is not adequately identifying all women who would benefit most from diet and/or physical activity weight management interventions, and some women are receiving expensive and time-consuming additional care that is not required. A meta-analysis of observational data, linking early pregnancy adiposity and GDM showed that women with GDM had significantly increased waist circumference (mean difference(MD): 6.18 cm 95% CI 3.92 to 8.44), waist-to-hip ratio (MD: 0.03 95% CI 0.02 to 0.04) and neck circumference (MD: 0.77 cm 95% CI 0.28 to 1.26).[30] The findings from this review suggest that adiposity markers, alternative to BMI, may have utility in the pregnant population for identifying women who are at increased risk of developing adverse outcomes. However, this meta-analysis did not compare the utility of these alternative measures to BMI. Targeting weight management interventions based on individual levels of adiposity may be more beneficial, compared with BMI. Measures that can be used to assess adiposity include circumference measurements (eg, waist), skinfold thicknesses and calculable indices (eg, waist-to-hip ratio).[31 32] Different types of adiposity including visceral and subcutaneous can be determined by ultrasound and bioelectrical impendence.[32]

This research aims to address a gap in the knowledge and is completely novel; in terms of the targeting interventions in pregnancy based on alternative measures of adiposity to BMI for the prevention of GDM and reduction of GWG. We plan to conduct an IPD meta-analysis to evaluate the differences in effectiveness of weight management interventions, by subgroups of adiposity and using adiposity as a continuous measure. The results of this IPD meta-analysis could inform whether targeting future interventions based on alternatives measures of individual adiposity rather than BMI would confer a benefit in terms of preventing GDM and reducing GWG.

Objectives

Primary

- To evaluate, by IPD meta-analysis, the effectiveness of targeting weight management interventions for the prevention of GDM based on alternative measures of adiposity.
- To evaluate, by IPD meta-analysis, the effectiveness of targeting weight management interventions for the reduction of GWG based on alternative measures of adiposity.

Secondary

- Explore GWG as both a continuous and categorical outcome.
- Determine the impact of the gestational age that adiposity was measured and the effectiveness of interventions.
- To perform subgroup analyses on the combined effect of adiposity and maternal ethnicity.
- To explore the combined effect of adiposity and maternal age.
- Where possible, perform subgroup analysis based on type of weight management intervention.

METHODS/DESIGN

Reporting of this protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[33] The protocol has been registered on PROSPERO, the International Prospective Register of Systematic Reviews (CRD42021282036). The reporting of the IPD meta-analysis will use the PRISMA-IPD reporting statement.[34]

Patient and public involvement

Patients have been involved with this work throughout and have informed design, outcome selection and reporting.

Literature search

This IPD meta-analysis will use data from the International Weight Management in Pregnancy (i-WIP) collaboration.[35] Literature searches for i-WIP were conducted in October 2013, March 2015, February 2017, February 2020 and March 2021 to identify potentially relevant trials.[36 37] The Seven databases searched were Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Review of Effects, Cochrane Central Register of Controlled Trials and Health Technology Assessment Database. Two reviewers screened the results of searches independently. Inclusion and exclusion criteria for inviting to the i-WIP collaboration are previously described.[36] Inclusion criteria were randomised controlled trials that recruited women with BMI>18.5 kg/m^2 to diet and/or physical activity interventions; interventions commenced during pregnancy; the effect of the intervention was compared against no intervention or standard antenatal care; and trials had to report maternal or infant outcomes. Exclusion criteria were trials that targeted women with gestational diabetes at baseline; reporting of only non-clinical outcomes; and published before 1990. Further inclusion and exclusion criteria will be applied for this IPD meta-analysis study. We will include trials that reported at least one adiposity measure (eg, waist circumference, skinfold thicknesses, bioelectrical impedance), in addition to BMI, in early pregnancy. For the purposes of this study, early pregnancy is defined as before 20 weeks' gestation. The trials must report GDM and/or GWG as an outcome. We will exclude trials that only collected BMI and reported no alternative adiposity measures, or trials that only recorded adiposity measures beyond 20 weeks' of gestation (table 1).

Identifying trials that recorded adiposity data

Two strategies will be used to identify trials that recorded adiposity measures in early pregnancy. For trials that have shared IPD with the i-WIP collaborative group, a survey will be circulated to authors requesting details on which adiposity measures had been collected and at what week of gestation. In the case of no response to the first contact, a total of three follow-up emails will be sent to maximise responses.[38] In addition, published trial protocols and their online supplemental file will be reviewed to

Table 1 Structured question for IPD meta-analysis

Component	Description
Population	Pregnant women with a BMI>18.5 kg/m^2 and recording of adiposity measure(s) prior to 20 weeks' gestation (eg, waist circumference, skinfold thicknesses)
Interventions	Diet or physical activity or combined intervention initiated in pregnancy prior to 24 weeks' gestation
Comparison	No intervention or standard antenatal care
Main outcomes	► GDM defined within in the study by established criteria. ► GWG as a categorical variable as defined by the NAM GWG guidelines
Other outcomes	► GWG as a continuous outcome ► The effect of maternal age ► The effect of maternal ethnicity
Study design	Randomised controlled trial

BMI, body mass index; GDM, gestational diabetes mellitus; GWG, gestational weight gain; IPD, individual patient data; NAM, National Academy of Medicine.

identify reported collection of adiposity measures. Where trials were identified from the systematic review and have yet to share IPD with the i-WIP collaboration, only a protocol review will be conducted. After the trials which had reported additional adiposity variables are identified, trial authors will be invited to share their IPD for these additional measures to the database.

Outcome measures

The primary outcomes are GDM and GWG (continuous). We will use the definition of GDM as defined by each trial author. We will analyse GWG as a continuous variable, measured by absolute change in weight (kg). For the secondary outcomes, we will analyse GWG as a categorical variable using criteria defined by the NAM (inadequate, adequate or excessive) for the corresponding preconception BMI.[12]

Where possible, we will perform subgroup analysis to look at the effect of maternal ethnicity, maternal age and intervention type. Maternal ethnicity and age will be explored as categorical variables, using previously described ethnic groups and age ranges[39] to explore their relationship between adiposity variables, outcome of interest (GDM or GWG) and intervention effect. Exploration of intervention type, mode of delivery, behavioural change techniques, will be conducted using the TIDiER framework.[40]

Study quality assessment and data collection

The i-WIP team use the Cochrane Collaboration risk of bias tool to score the quality of IPD from trials.[41] The same methods will be applied to any new studies that meet the inclusion criteria from updated literature searches.[39] Where required, trial authors will be contacted for trial protocols and additional details to assess potential bias.

We will request additional IPD on adiposity measures from existing i-WIP collaborators and newly identified trials. Data will be subject to Processing, Replication, Imputation, Merging and Evaluation prior to the two-stage meta-analysis.[42] This ensures the dataset is standardised, that the descriptive statistics in publications match the IPD, missing variables are dealt with appropriately and trials are then merged into a master data sheet.[42] Where descriptive statistics are not included in publications or online supplementary materials, range and sense checks will be performed on variables, as well as integrity checks. Any discrepancies will be resolved with trial authors.

Sample size consideration

This IPD meta-analysis will be limited by data availability, with final participant numbers are unable to be stated until trial screening has been completed.

Data analysis

Overall effect

The effectiveness of weight management interventions to prevent GDM and reduce GWG based on early pregnancy adiposity will be assessed using IPD meta-analytical framework. GDM will be defined as per each trial author and analysed as a binary outcome. GWG will be analysed as a continuous variable, and as a categorical variable by applying the NAM GWG criteria (inadequate, appropriate or excessive).[12] These will be analysed based on adiposity at baseline.

For each outcome (GWG continuous and categorical; GDM), a two-step IPD meta-analysis using a random treatment effect approach will be used, which accounts for differences between the interventions used in each trial. The overall effects of interventions on GDM and GWG will be summarised, then differential effects by adiposity measure will be summarised as a treatment–covariate interaction. A random treatment effects approach allows for inter-study heterogeneity in intervention effect, which would be expected given the different interventions employed by each study.[43]

In the first stage, each study will be analysed to obtain treatment effect and its variance. This will be achieved by applying regression models; a logistic regression model will be applied to the analysis of GDM as a binary variable and GWG as an ordinal variable, this will produce an OR.[43] A linear regression model will be used for analysis of GWG as a continuous variable to produce a difference in means, this will reflect absolute change in weight (kg). Each effect will be measured so that the trials can be combined in the second stage.[43] The second stage of the IPD meta-analysis will then be performed. This will calculate the I^2 statistic, which estimates the proportion of total variability due to between-study heterogeneity and tau^2, which is an estimate of between-trial variance of treatment effect by applying the restricted maximum likelihood method.[44] Once the two-stage IPD meta-analysis model has been estimated, 95% CIs will be calculated for the summary treatment effect. The Hartung-Knapp Sidiki-Jonkman approach will be used as it accounts for uncertainty in variance estimates. This analysis approach will be applied to the effect on GDM and GWG, as both a continuous and categorical variable.

Differential effect by subgroup (treatment–covariate interactions)

The effect of different adiposity measures will be analysed as a treatment–covariate interaction. This will be undertaken by extending the two-stage meta-analysis frameworks to include and summarise the treatment–covariate interactions terms. Where possible, we will perform subgroup analysis on maternal ethnicity and maternal age to assess potential modification of intervention effect, as both are associated with GDM and GWG. Maternal ethnicity and maternal age will be analysed as categorical variables. They will be categorised in line with previous reporting by the i-WIP collaboration.[39]

Potential sources of bias

Small study effects, which can occur due to publication bias, will be explored by generating contour-enhanced funnel plots with appropriate statistical tests. Where IPD is unavailable we will extract aggregate study-level data, where available, and incorporate with the IPD using a

two-stage random effects model.[45] We will undertake sensitivity analysis and exclude trials not at a low risk of bias to ascertain if conclusions change when all studies are included. The Grading of Recommendations, Assessment, Development and Evaluations approach will be used to grade the evidence in the IPD meta-analysis.[46]

Dealing with missing variables

Different strategies for dealing with missing data will be considered. Multiple imputation will be used to impute partially missing variables within each study using a missing at random assumption. If there are systematically missing variables then, where plausible, these will be imputed by borrowing information across studies while allowing for heterogeneity and clustering in a multilevel imputation model.[47]

Discussion

This IPD meta-analysis aims to evaluate the differences in effectiveness of weight management interventions based on alternative adiposity measurements in early pregnancy and the effects on GDM and GWG. Results have the potential to influence how weight management interventions in pregnancy are targeted in antenatal care, for the prevention of GDM and reduction of GWG, as it may be beneficial to prioritise intervention delivery based on individual adiposity rather than BMI alone. To our knowledge, this is the first time that evaluating weight management interventions in early pregnancy based on individual adiposity, not BMI, has been conducted.

Previous IPD meta-analysis produced from the i-WIP collaborations data suggested that weight management interventions led to a MD in GWG of −0.7 kg (95% CI −0.92 kg to −0.48 kg) compared with control.[48] When IPD was combined with study-level aggregate data not included in the IPD meta-analysis, the MD of GWG was −1.1 kg (95% CI −1.46 kg to −0.74 kg) in women receiving a weight management intervention, compared with control.[39 48] There was no significant treatment–covariate interaction between baseline BMI and effect of interventions on GWG.[39] Weight management interventions had a trend towards a reduction in odds of GDM, across all BMI categories; however, this was not found to be statistically significant (OR: 0.89, 95% CI 0.72 to 1.10).[39 48]

Reanalysing these data based on early pregnancy adiposity instead of BMI may provide new insights into the effectiveness of weight management interventions for prevention of GDM and reduction of GWG. This may help to inform future research, guidelines, and routine practice for weight management interventions during delivered pregnancy. If adiposity is found to be an important factor during pregnancy, then this would also inform future adiposity research in the preconception, postnatal and interpregnancy periods.

Consistent evidence of reductions in GWG from pregnancy weight management interventions has been reported.[49] A recent systematic review of meta-analyses synthesised evidence from systematic reviews reporting the effect of behaviour change interventions in pregnancy on GWG.[49] Findings from 66 meta-analyses from 36 systematic reviews demonstrated that diet and physical activity interventions had a general pattern of reduction in GWG, with 53 meta-analyses showing a significant reduction in mean GWG ranging from −0.21 kg (95% CI −0.34 to −0.08) to −5.77 kg (95% CI −9.34 to −2.21). This was consistent regardless of intervention type (ie, diet only, physical activity only, or combined), although effect sizes were largest for diet only interventions. When stratifying interventions based on BMI, the largest reductions in GWG were seen in women with overweight or obesity.

However, the evidence base for prevention of GDM by weight management interventions is inconsistent. The same systematic review of meta-analyses identified 29 systematic reviews reporting 59 meta-analyses for GDM.[49] The direction of effect was that women receiving diet and/or physical activity interventions had reduced odds of developing GDM compared with controls; however, inconsistencies in statistical significance were present. Larger effect sizes and a higher proportion of statistically significant reductions in GDM were seen among interventions that had diet only or physical activity only components, whereas combined interventions were less likely to have statistically significant reductions in GDM. The inconsistencies in the effectiveness of interventions for the preventions of GDM are echoed by an overview of systematic reviews published by the Cochrane collaboration, that included 11 reviews with evidence from 71 trials (23,154 women).[50] Results suggested that dietary intervention alone had low-quality evidence, with unknown benefit or harm compared with standard care (RR 0.60, 95% CI 0.35 to 1.04). Similar findings were found for physical activity interventions (RR 1.10, 95% CI 0.66 to 1.84). The effect of combined interventions showed possible benefit compared with standard care (RR 0.85, 95% CI 0.71 to 1.01).[50] The results of these two systematic reviews show different patterns of potential benefit of different components of diet or physical activity or combined interventions for the prevention of GDM; highlighting the conflicting results across the evidence base. In addition to the potential influence of maternal adiposity, the inconsistencies in the evidence may partly be due to the differences in the content or mode of delivery of the interventions. For example, there is evidence for the beneficial effects of the Mediterranean diet significantly reducing the odds for developing GDM by 25%–35%.[51 52]

Finding effective interventions for reducing GWG and preventing GDM are a high priority given their immediate and long-term effects on both women and their infants. Investigating if individual adiposity in early pregnancy may better select women for these weight management interventions would potentially allow for more effective targeting of interventions, improving health outcomes for women and their infants and, healthcare provision.

Findings from a Delphi study conducted by the i-WIP collaboration cited GDM as a maternal outcome that was critical to patient care.[53] GWG was not included in

the final list as it was considered a surrogate of maternal morbidity.[53] However, GWG is an important outcome to focus on given the high prevalence of excessive GWG, which was estimated at 56% of women in a recent UK study.[54] Women who gain excessive weight in pregnancy are also more likely to retain this weight, increasing risk of obesity across the life course, as well as having infants who develop obesity; making reducing GWG a public health priority for research.[55 56]

A strength of the i-WIP collaboration is that it includes a broad range of trials from international collaborators, improving the generalisability and applicability of findings to different populations. Given the novel nature of our IPD meta-analysis, there are some limitations with the current evidence base. First, the potential differences in how adiposity measures were recorded and on which gestational week vary across trials. Using a cut-off of 20 weeks of gestation was determined pragmatically to try to maximise sample size but to be early enough in gestation that (1) body composition has not been remarkably altered by pregnancy and (2) an intervention could theoretically be started prior to GDM screening. However, if adiposity measures were assessed closer to 20 week's gestation there is the argument that implementation of an intervention would have a very small effect, if any, on the likelihood of GDM, given that screening and diagnosis occurs between weeks 24 and 28 of gestation. Second, differences in how GDM is assessed and diagnosed may vary across trials, with i-WIP using trial-specific definitions of GDM.[39] Total GWG is dependent on what gestational age the first and final weight measurements are taken, to calculate total GWG. NAM guidelines for total GWG are based on preconception weight and weight at the time of delivery; therefore, using weight measurements calculated at different time periods leading to inaccurate interpretations of the recommended GWG ranges.[57] Third, differences in the type and intensity of interventions and their modes of delivery make it challenging to directly apply findings clinically.

If adiposity measures are found to be important in targeting weight management intervention in pregnancy, future work may focus on the cost-effectiveness of using adiposity measures to target interventions for the prevention of GDM and reduction of GWG. This would be of particular interest given that women with overweight and obesity in pregnancy have increased service usage and costs of 23% and 37%, respectively.[58] Additionally, evidence from a systematic review suggested that the incremental cost of GDM ranged from €263 to €13 680.[59] The high level of heterogeneity between the 16 studies, and methods used make it challenging to draw appropriate conclusions, providing further grounds for the cost-effectiveness of interventions to be explored.

ETHICS AND DISSEMINATION

This is an evidence synthesis project involving IPD meta-analysis of anonymised data sets, no further ethical approvals are required. The guidance on IPD storage and management of data will be adhered to.[39] Findings will be published in peer-reviewed journals, included in a PhD thesis, and other appropriate dissemination informed by patient and public involvement and stakeholder engagement activities (eg, policy briefings). Findings will also be made accessible to patients and the public as well as relevant charities.

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