Does prepregnancy weight change have an effect on subsequent pregnancy health outcomes? A systematic review and meta-analysis

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Abstract:

International guidelines recommend women with an overweight or obese body mass index (BMI) aim to reduce their body weight prior to conception to reduce the risk of adverse perinatal outcomes. Recent systematic reviews have demonstrated that interpregnancy weight gain increases women's risk of developing adverse pregnancy outcomes in their subsequent pregnancy. Interpregnancy weight change studies exclude nulliparous women. This systematic review and meta-analysis was conducted following MOOSE guidelines and summarises the evidence of the impact of preconception and interpregnancy weight change on perinatal outcomes for women regardless of parity. Sixty studies met the inclusion criteria for this review and reported 34 different outcomes. We identified a significantly increased risk of gestational diabetes (OR 1.88, 95% CI 1.66, 2.14, I^2=87.8%), hypertensive disorders (OR 1.46 95% CI 1.12, 1.91, I^2=94.9%), preeclampsia (OR 1.92 95% CI 1.55, 2.37, I^2=93.6%), and large-for-gestational-age (OR 1.36, 95% CI 1.25, 1.49, I^2=92.2%) with interpregnancy and preconception weight gain. Interpregnancy weight loss was significantly associated with increased risk for small-for-gestational-age (OR 1.29 95% CI 1.11, 1.50, I^2=89.9%) and preterm birth (OR 1.06 95% CI 1.00, 1.13, I^2=22.4%). Our findings illustrate the need for effective preconception and interpregnancy weight management support to improve pregnancy outcomes in subsequent pregnancies.

Abbreviations:
BMI – Body mass index; GDM – Gestational diabetes mellitus; GWG – Gestational weight gain LGA – Large-for-gestational-age; MOOSE – Meta-analysis of observational studies; OR – Odds ratio; CI – Confidence intervals; SGA – Small-for-gestational-age; VBAC – Vaginal birth after caesarean

Introduction:

The positive association between maternal preconception body mass index (BMI) and adverse perinatal outcomes is well established.[1-3] Women who have obesity are at risk for pregnancy complications, including gestational diabetes (GDM), hypertensive disorders of pregnancy such as preeclampsia, and excessive gestational weight gain (GWG).[1,4] Pregnancy weight management guidelines suggest that women with an overweight or obese BMI (≥25.0 kg/m^2) should aim to reduce their body weight prior to conception to have a BMI within the recommended range (18.5-24.9 kg/m^2).[5-7] As the prevalence of maternal obesity increases,[8] more women of reproductive age may be attempting weight loss before conception as recommended by prenatal healthcare providers to reduce the risk for complications. Although there is evidence to show that preconception weight loss can improve fertility outcomes,[9] there is a paucity of knowledge on the effect of preconception weight change (loss or gain) on the development of subsequent perinatal complications.

Recently, three systematic reviews were completed evaluating the effect of interpregnancy weight change (i.e., the weight gain or loss between two pregnancies) on perinatal outcomes in subsequent pregnancies.[10-12] Consistently, authors of these reviews reported that interpregnancy weight gain was associated with a higher risk for large-for-gestational-age (LGA) newborns and GDM in the second pregnancy, whereas interpregnancy weight loss decreased the risk for LGA newborns.[10-12] Furthermore, compared to women who maintained their prepregnancy BMI across pregnancies, those who gained weight between pregnancies were at greater risk of complications.[10-12] Authors concluded that both interpregnancy weight gain and maternal BMI are predictive factors for perinatal complications in subsequent pregnancies.[10-12]

The existing reviews which focus on interpregnancy weight change, by their nature, exclude primiparous women. Given the increasing prevalence of obesity among women of reproductive age and guideline recommendations to lose weight before pregnancy, women may have been attempting to lose weight in advance of their first pregnancy as well as between pregnancies.[8,13-15] It is estimated that approximately 42-44% of the adult general population attempt weight loss annually. Women are twice as likely as men to report weight loss or weight management efforts.[16] Therefore, in addition to interpregnancy weight change, first-time mothers may also experience preconception weight loss or gain, which may influence the development of perinatal complications. This systematic review aimed to explore the impact of weight change experienced before any pregnancy (i.e., first or subsequent pregnancy) on perinatal outcomes. This review extends the work performed by others that assessed interpregnancy weight change only.[10-12] Our goal is to provide information on the impact of weight change on pregnancy outcomes for all women regardless of parity.

Methods:

Search Strategy:

This systematic review and meta-analysis was conducted in accordance with the recommendations for meta-analysis of observational studies in epidemiology (MOOSE)[17] and the protocol was registered on PROSPERO (CRD42019156949). The following databases were searched on October 23rd 2019, and updated on August 27th 2020: MEDLINE, Cochrane Reviews, Embase, and Scopus using keywords and MeSH headings for the terms preconception, weight change, and pregnancy (Table S1). Searches were limited to human studies, and no date or language restrictions were applied. In line with MOOSE guidelines, systematic reviews of

observational studies require supplementary searches in addition to databases to comprehensively search for all relevant published data.[17] Therefore, two reviewers (RHL and SD) hand searched the reference lists of all related systematic reviews and included studies, and completed citation searches for all studies that met the inclusion criteria using Google Scholar Citations (Tables S2 and S3). If studies were identified through citation and reference list searches, they were subject to further reference list and citation searches and this process was repeated until no new studies were identified. If required, authors of included studies were contacted for additional data needed for the meta-analysis (Table S4).

Inclusion Criteria:

Inclusion criteria were peer-reviewed observational studies (cohort, case-control, or cross-sectional designs) with retrospective or prospective design, reporting the association between the exposure variable (preconception or interpregnancy weight change) and outcome variable (perinatal outcome). For the purpose of this review, data reported as preconception relates to weight change before any pregnancy for women of any parity that is not directly related to any previous pregnancies, whereas data for interpregnancy weight change refers specifically to weight change between two pregnancies. Weight change included weight loss or gain, and could be reported in any units (e.g., kg, BMI) and any perinatal health outcomes (e.g., GDM, GWG, preterm delivery, maternal mental health) were included.

Data Extraction:

Duplicate citations of the same study were excluded using the deduplication feature on Endnote software,[18] and remaining citations were transferred to Covidence[19] for screening. Titles and abstracts were initially screened to identify studies which potentially met the inclusion

criteria, followed by a full text assessment against the inclusion criteria by two independent reviewers (TSN; SCSS). Studies which met the inclusion criteria but reported data from the same cohort were included if they reported different outcomes, otherwise duplicate data were excluded (Table S5). If studies reported duplicate data on the same outcome, we selected the study that reported the largest sample size and longest recruitment period for inclusion. Exclusions are reported in Table S6.

Standardized data extraction tables were developed for this review and included the following items: exposure, exposure reference group, exposure category, sample size for comparisons, perinatal outcome, measures of association, adjustments made to analyses. The following study characteristics were also extracted: study period, data source/registry, country of study, total sample size, inclusion and exclusion criteria, study objectives, definition of preconception or interpregnancy weight change, maternal age and BMI. Quality assessments were completed using the Newcastle-Ottawa scale for cohort and case-control studies (Tables S7 and S8).[20] The Newcastle-Ottawa scale assesses information and selection bias, and confounding variables. Data extraction and quality assessments were completed by two independent researchers for each included study (TSN; SCSS; TN; RHL).

Analysis:

Studies were pooled in a meta-analysis to estimate the odds-ratio (OR) and a 95% confidence interval (CI) when there were at least two studies reporting the same outcome. Meta-analysis of weight gain and weight loss were carried out separately. Sub-group meta-analysis was carried out, where possible, to compare the pooled effect sizes and heterogeneity for different time points of data collection (i.e., interpregnancy or preconception) and for different measures of weight change. The weight measurement subgroups included BMI change or "other

measures" of weight change (e.g. kg, pounds, percent change), and were further stratified where possible based on whether or not there was an upper limit to the weight change. Supplementary meta-analyses were carried out to explore the combined association between weight change and maternal BMI. I^2 values of 25%, 50%, and 75% were used to indicate low, moderate and high levels of heterogeneity.[21] Sources of heterogeneity were initially explored through subgroup meta-analysis, and when high levels of heterogeneity remained meta-regression was carried out. Variables identified *a-priori* to be included in meta-regression for each outcome were related to study design (e.g. sample size, prospective or retrospective, adjustments made in the analysis), population (e.g. country of study, time period of study), outcome definition and quality. Publication bias was investigated using Egger's test and funnel plots. Sensitivity analysis was performed for each meta-analysis (including the overall pooled estimates and subgroup meta-analyses) to explore the effect of any individual results on the pooled effect size. Additionally, if there were three or more subgroups then sensitivity analysis was carried out excluding each subgroup to explore the potential implications of pooling different time periods and measures of weight change. All analysis was conducted in Stata v16.[22] If meta-analysis was not possible, studies were synthesized narratively in accordance with Popay et al.[23] guidance on the conduct of narrative synthesis in systematic reviews. Data were tabulated, transformed if possible where required (e.g. calculation of ORs using frequency data reported in the papers). Data were grouped into thematic categories, and the associations between preconception or interpregnancy weight change and perinatal outcomes was described including the estimate of effect size and variance.

Results:

Study Selection and Characteristics:

Database searches identified 3,149 studies for screening following deduplication, and supplementary searches identified a further 4,651 studies to be screened; of which 60 met the inclusion criteria and reported unique data (Fig S1). The included studies reported both preconception weight change (n=12) and interpregnancy weight change (n=48), and the following outcomes: GDM (n=22), any hypertensive disorder (n=19), preeclampsia (n=7), preterm birth (n=14), LGA (n=16), SGA (n=13), cesarean delivery (n=13), stillbirth and neonatal mortality (n=6), vaginal birth after caesarean (VBAC) (n=4), postnatal hemorrhage (n=2), Apgar scores (n=2), birthweight z-scores (n=2), any congenital malformation (n=2), and single studies for spina, bifida, gastroschisis, conotruncal birth heart defects, cleft lip, GWG, placental weight, neonatal intensive care unit admission, $3^{rd}/4^{th}$ degree tear, episiotomy, shoulder dystocia, hypoglycemia, birth trauma, respiratory distress, infant anthropometrics, meconium aspiration, neonatal seizures, pregnancy loss, induced labour, instrumental delivery, and maternal morbidity. Studies were published between 1999 and 2020, with sample sizes ranging from 72 to 526,435. The studies were carried out in the US (n=36), Australia and Sweden (n=6 each), England, France, Ireland and Scotland (n=2 each), Belgium, Canada, Denmark and Norway (n=1 each) (Table S9).

The quality of included studies ranged between 3-8 stars for cohort studies (n=38 high quality, n=12 medium quality, n=0 low quality), and 4-8 stars for case control studies (n=7 high quality, n=3 medium quality, n=0 low quality) (Table S10 and S11). Cohort studies had the highest scores on the selection of the non-exposed cohort being the same community as exposed cohort (question 2), the representativeness of the exposed cohort being either truly or somewhat representative to average maternal population in the community (question 1), and having an adequate follow-up period for the outcome of interest (question 6). The lowest scoring criteria

related to the ascertainment of exposure (question 3) which generally used self-reported measures. The highest scores in case control studies were for the use of the same method of ascertainment for cases and controls (question 7), and same non-response rate for both groups (question 8). The lowest scoring criteria were for the definition of controls having no description of the source (question 4) and, similar to the cohort studies, the ascertainment of exposure was mostly self-reported (question 6).

Meta-analysis was possible for GDM, hypertensive disorders of pregnancy, preeclampsia, LGA, small-for-gestational-age (SGA), caesarean delivery, vaginal birth after cesarean (VBAC), stillbirth, preterm delivery, low Apgar score, and postpartum hemorrhage. It was possible to stratify meta-analysis for most outcomes by preconception and interpregnancy weight gain; however, for weight loss there were only preconception data available for LGA and the remaining meta-analyses are limited to the interpregnancy period. The additional data that could not be pooled into meta-analysis were grouped into three themes relating to neonatal outcomes, labour and delivery outcomes, and maternal outcomes and are reported narratively.

Meta-analysis GDM:

There were 22 studies that reported associations between weight change and GDM (557,017 women)[24-45] and 19 could be pooled in the meta-analysis;[24-43] 18 studies could be pooled for meta-analysis of the association between GDM and weight gain in the preconception and interpregnancy periods,[25-42] and 13 studies for interpregnancy weight loss.[26,29,30,32,33,35-39,41-43] Overall women who gained weight before or between pregnancy were significantly more likely to develop GDM than those whose weight remained stable (OR 1.88, 95% CI 1.66, 2.14, I^2=87.8%, Figure 1). Conversely, women who lost weight between pregnancies were

significantly less likely to develop GDM compared with women whose weight remained stable (OR 0.75, 95% CI 0.62, 0.92, I^2=87.2%, Figure 2).

Figure 1. Meta-analysis of the association between GDM and prepregnancy and interpregnancy weight gain

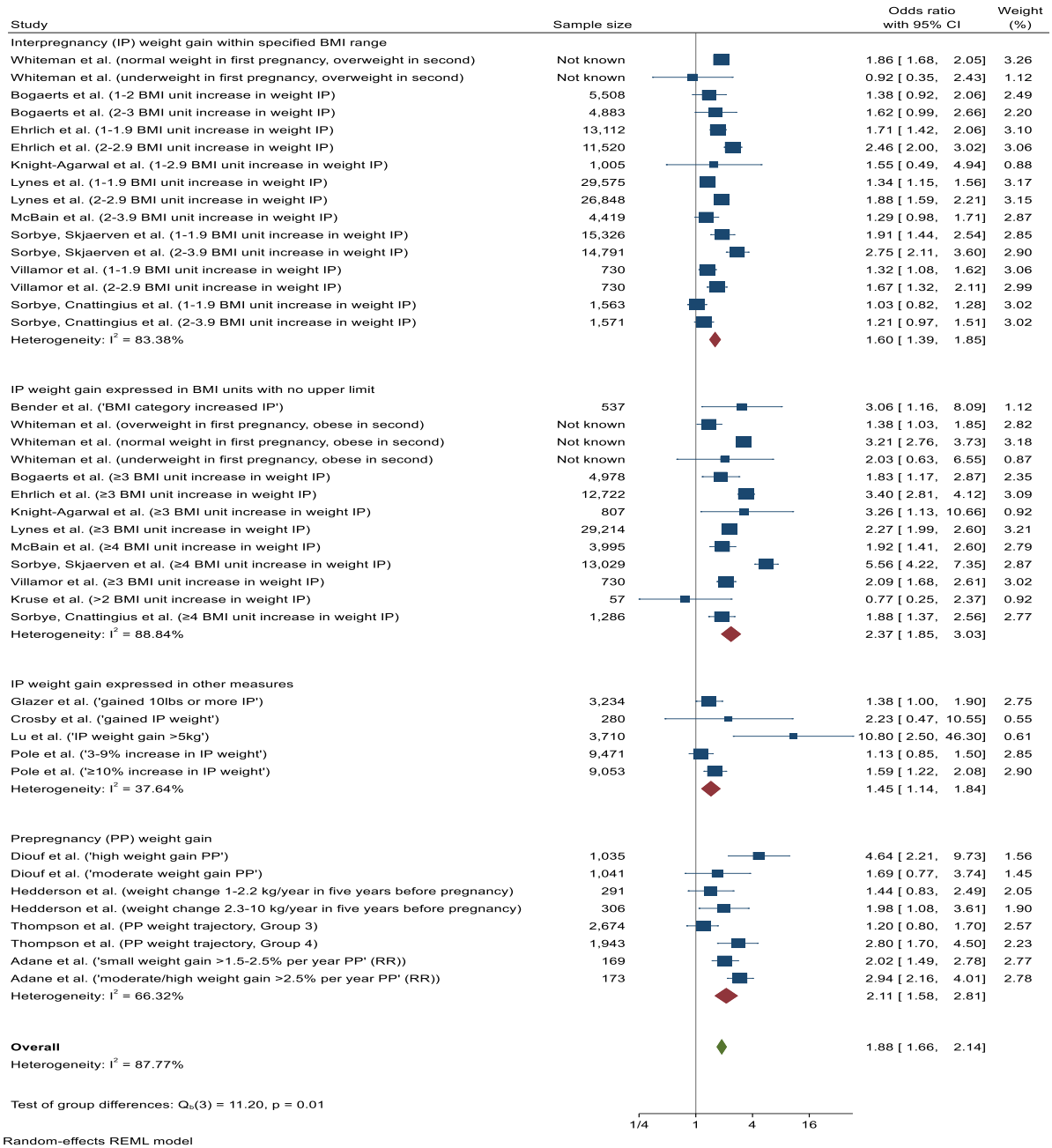
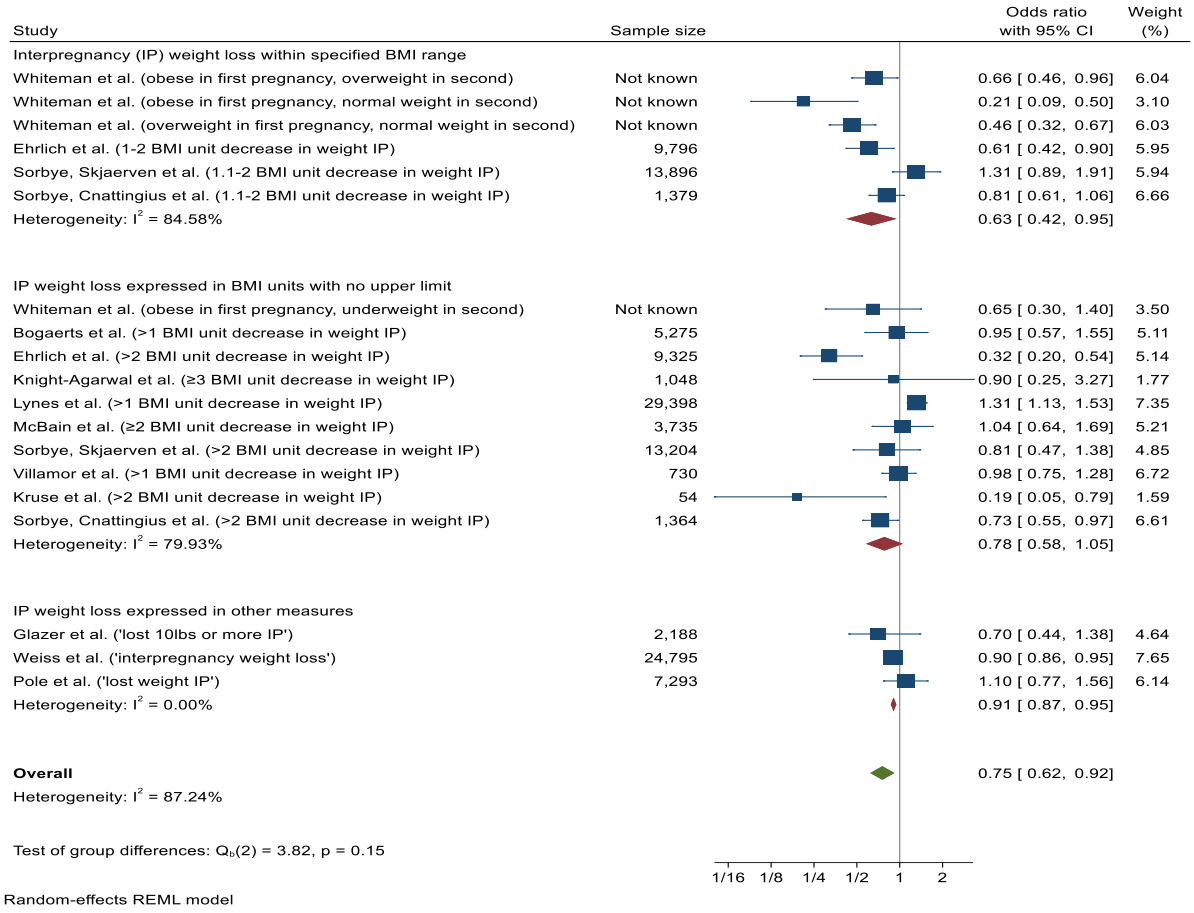


Figure 2. Meta-analysis of the association between GDM and prepregnancy and interpregnancy weight loss



Four studies could be pooled for meta-analysis stratified by BMI category for interpregnancy weight gain[26,29,36,41] and four for weight loss;[29,36,41,43] no data were available for preconception weight change. There was a significantly increased odds of GDM associated with interpregnancy weight gain for both BMI subgroups, although higher among women with a BMI <25kg/m^2 than for BMI>25kg/m^2 (Figure 3a). Interpregnancy weight loss was associated with a significant reduction in GDM for both BMI subgroups (Figure 3b).

Figure 3a. Meta-analysis of weight gain and GDM stratified by maternal BMI

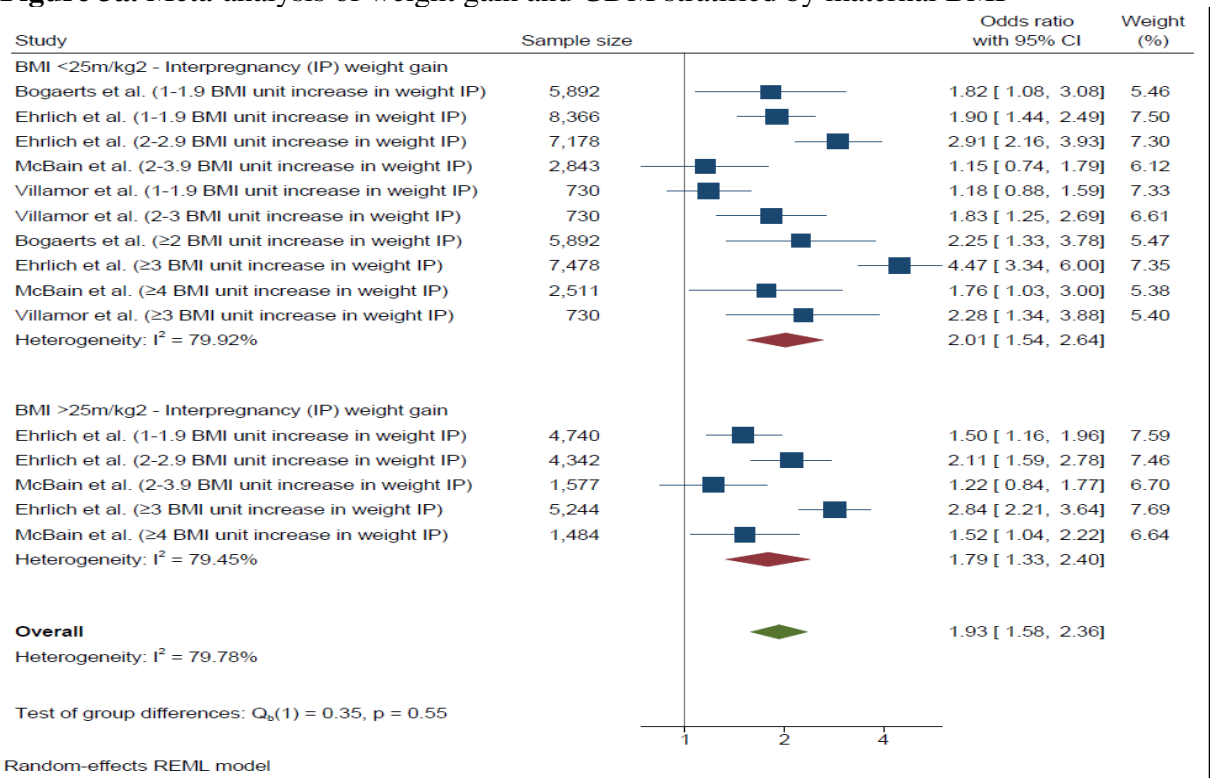
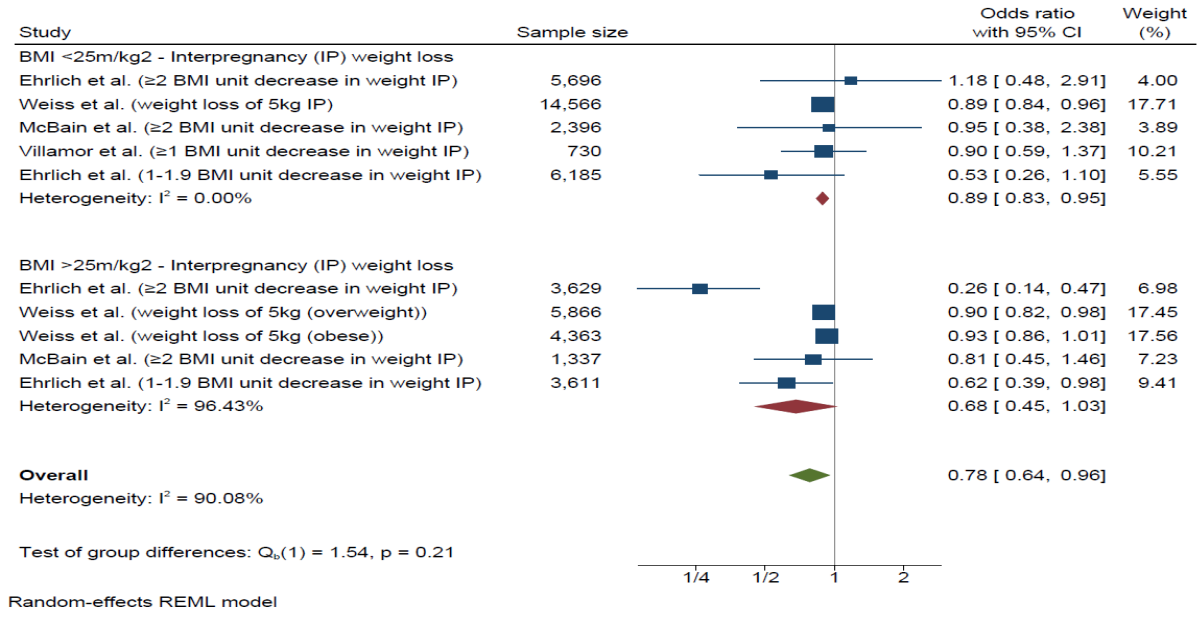


Figure 3b. Meta-analysis of weight loss and GDM stratified by maternal BMI



Meta-analysis hypertensive disorders of pregnancy and preeclampsia:

There were 19 studies (451,127 women) that reported associations between weight change and hypertensive disorders of pregnancy and all were included in the meta-analysis.[25-28,32,35-37,40,41,43,46-53] There were 14 studies included in the meta-analysis of weight gain preconception or interpregnancy and hypertensive disorders (Fig S3a),[25-28,32,35-37,41,46-50] and seven for preeclampsia (Fig S4a);[35,40,41,50-53] both showed significantly increased odds compared with women whose weight remained stable (OR 1.46 95% CI 1.12, 1.91, I^2=94.9% and OR 1.92 95% CI 1.55, 2.37, I^2=93.6% respectively). The significant results remained in all subgroup analysis for preeclampsia, whereas for hypertensive disorders only the results for BMI change were significant and not for "other measures" of weight change.

There were nine studies included in the meta-analysis for interpregnancy weight loss and hypertensive disorders (Fig S3b)[26,32,35-37,41,43,47,50] and five for preeclampsia (Fig S4b),[35,41,50,52,53] both of which showed no significant difference between women who lost weight and those whose weight remained stable in the overall pooled analysis (OR 0.95, 95% CI 0.82, 1.10, I^2=58.5% and OR 1.23, 95% CI 0.81, 1.85, I^2=92.2% respectively). However, there was a significant decrease in odds of hypertensive disorders in the subgroup analysis for "other" measures of weight loss, and a significant increase in odds for preeclampsia in the weight loss within a specified BMI range subgroup, although this was using multiple data categories from a single study.

There were three studies that could be pooled for the meta-analysis of hypertensive disorders of pregnancy and interpregnancy weight gain stratified by maternal BMI,[26,36,41] and three for weight loss[36,41,43]. The increase in odds of hypertensive disorders associated with interpregnancy weight gain was only significant for BMI<25 kg/m^2 (OR 1.94, 95% CI 1.42,

2.64, I^2=59.9%) (Fig S3c), whereas there was only a significant reduction with interpregnancy weight loss for BMI>25kg/m^2 (OR 0.85, 95% CI 0.79, 0.93, I^2=27.8%) (Fig S3d).

Meta-analysis LGA:

There were 15 studies that reported associations between weight change and LGA (411,781 women);[25-28,36,41,43,48,50,54-59] all were pooled in the meta-analysis for weight gain, and 13 for weight loss[28-30,35,40,47,51,53,58,60,61,63,64].[25-27,32,36,43,48,50,55,57,58,60,6128-30,35,39,46,51,53,58,60,61,63,6428-30,35,39,46,50,52,57,59,60,62,63] There was a significantly increased odds of LGA when women gained weight preconception or interpregnancy compared with women whose weight remained stable (OR 1.36, 95% CI 1.25, 1.49, I^2=92.2%), which remained for all subgroups (Figure 4). There was no significant association between LGA and weight loss in the overall analysis (OR 0.91, 95% CI 0.81, 1.03, I^2=93.0%), and the association was only significant for one subgroup (other measures of interpregnancy weight loss with no upper limit, Figure 5). There were five studies that reported data that could be pooled in the BMI stratified analysis for LGA and interpregnancy and preconception weight gain,[26,27,36,41,59] and six studies for weight loss.[27,36,41,43,58,59] There was a significantly increased odds of LGA with preconception or interpregnancy weight gain for both BMI groups but a larger effect size was observed for BMI <25kg/m^2 (OR 1.31, 95% CI 1.21, 1.41, I^2=17.2%) than for BMI >25kg/m^2 (OR 1.14, 95% CI 1.02, 1.29, I^2=5.1%) (Fig S5a). There was also a significantly reduced odds of LGA and preconception or interpregnancy weight loss with similar effect sizes for BMI <25 kg/m^2 (OR 0.78, 95% CI 0.76, 0.81, I^2=0.01%) and >25kg/m^2 (OR 0.81, 95% CI 0.79, 0.84, I^2=0.02%) (Fig S5b).

Figure 4. Meta-analysis of the association between large for gestational age (LGA) and prepregnancy or interpregnancy weight gain

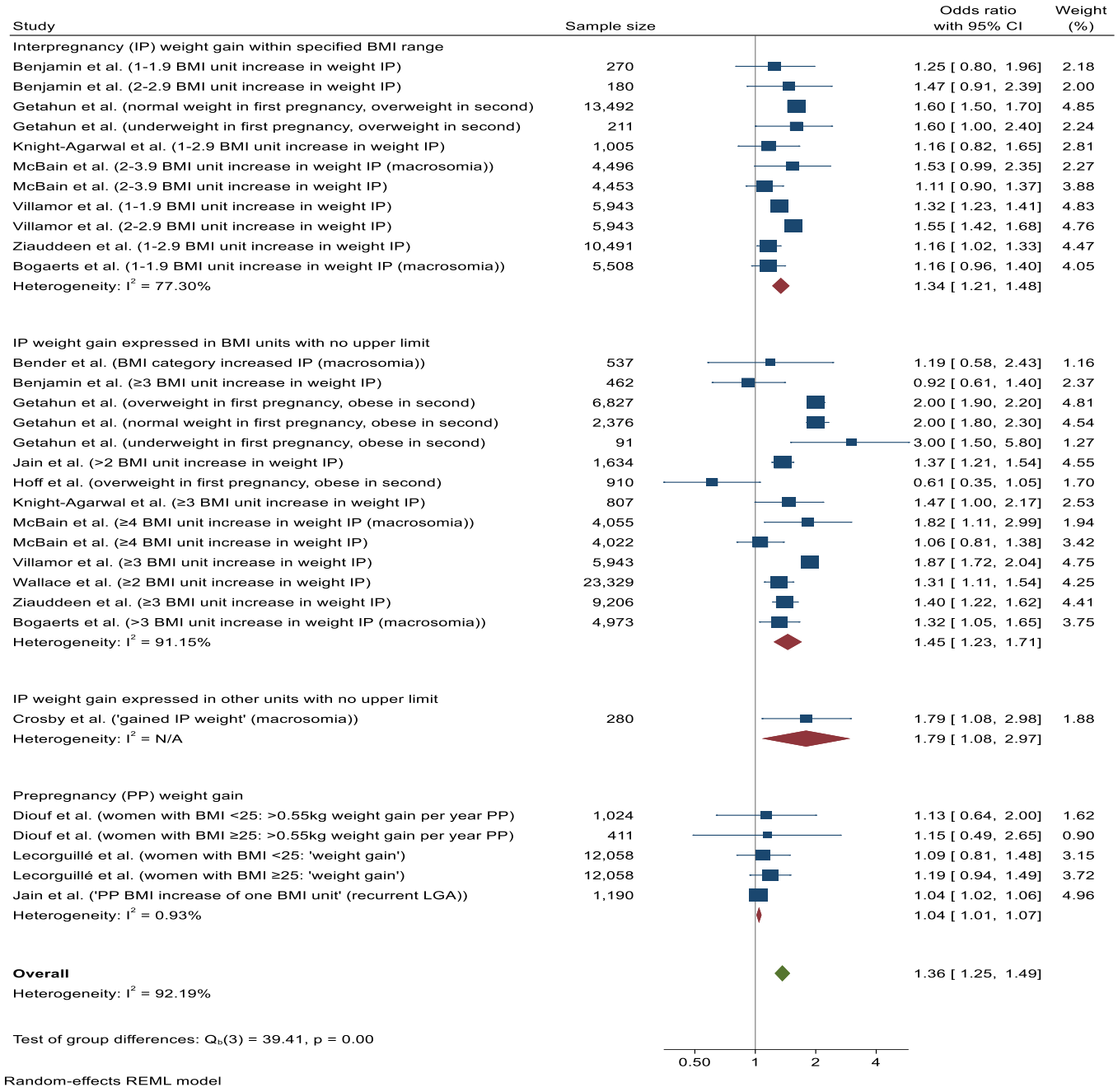
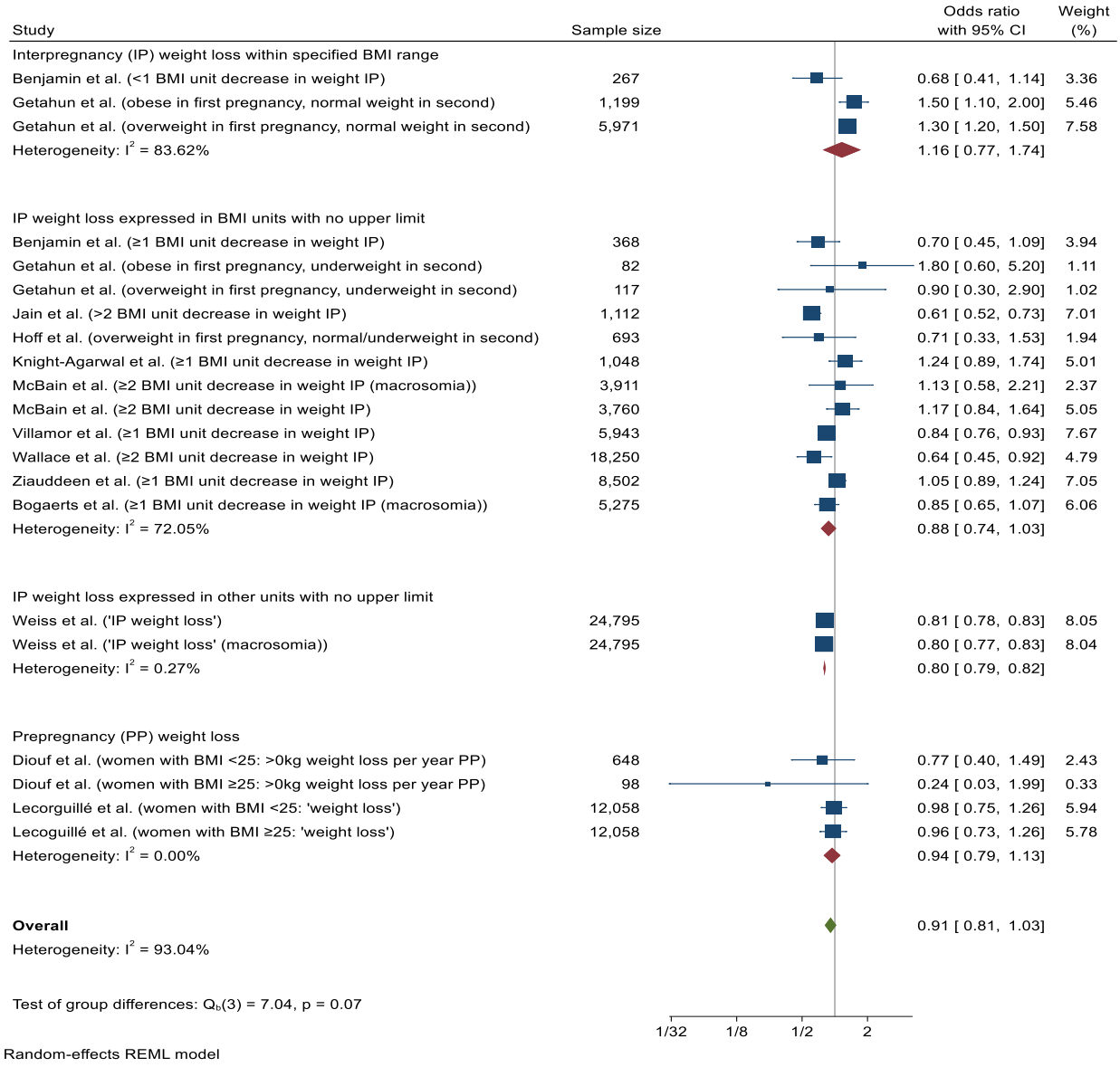


Figure 5. Meta-analysis of the association between large for gestational age (LGA) and prepregnancy or interpregnancy weight loss



Meta-analysis SGA:

There were 13 studies that reported the association between weight change and SGA (141,087 women);[25-27,32,36,43,48,50,55,57,58,60,61] 13 were pooled in the meta-analysis for weight gain [25-27,32,36,43,48,50,55,57,58,60,61] and 12 for weight loss. [25-27,32,36,43,48,50,55,57,60,61] There was no significant

association between weight gain and SGA in the overall pooled analysis (OR 1.00 95% CI 0.87, 1.14, I^2=62.3%) or subgroup analyses (Fig S6a); whereas there was a significantly increased odds for weight loss (OR 1.29, 95% CI 1.11, 1.50, I^2=89.9%), although this was not significant for the preconception subgroup (Fig S6b).

Two studies reported data that could be included in the BMI stratified meta-analysis for SGA and interpregnancy or preconception weight gain[27,36] and four for weight loss.[26,27,36,43] There was no significant association between weight gain and SGA for either BMI subgroup (Fig S6c), whereas there was a significantly increased odds for weight loss and SGA for women with a BM<25kg/m^2 (1.49, 95% CI 1.15, 1.92, I^2=90.7%) but not for BMI>25kg/m^2 (Fig S6d).

Meta-analysis caesarean delivery and VBAC:

There were 13 studies reporting associations between interpregnancy weight change and caesarean delivery (523,195 women); [26,28,32,35,37,41,43,45,48,50,62-64] 11 were included in meta-analysis for weight gain and weight loss.[26,32,35,37,41,43,48,50,62-64] There was a significantly increased odds of caesarean with interpregnancy weight gain (OR 1.34, 95% CI 1.22, 1.48, I^2=91.2%) (Fig S7a)., whereas there was no significant association for weight loss (OR 1.10, 95% CI 0.92, 1.31, I^2=93.7%) (Fig S7b). There were two studies that reported data which could be pooled into BMI stratified meta-analysis for interpregnancy weight gain,[26,41] and two for weight loss.[41,43] There was a significantly increased odds of caesarean and weight gain for both BMI subgroups with a greater effect size for BMI>25kg/m^2 than for BMI<25kg/m^2 (OR 2.04, 95% CI 1.41, 2.95, I^2=N/A and OR 1.14, 95% CI 1.02, 1.28, I^2=60.4% respectively) (Fig S7c). There was only a significantly reduced odds of caesarean delivery with interpregnancy weight loss for BMI>25kg/m^2 (OR 0.88, 95% CI 0.82, 0.96, I^2=58.6%) (Fig S7d).

Four studies reported data for VBAC (56,691 women)[32,35,65,66] and all could be pooled in the meta-analysis for interpregnancy weight gain and weight loss. There was a significantly reduced odds of successful VBAC and interpregnancy weight gain (OR 0.81, 95% CI 0.71, 0.92, I^2=58.3%) (Fig S8a), but not for weight loss (OR 0.98, 95% CI 0.86, 1.12, I^2=0%) (Fig S8b).

Meta-analysis stillbirth:

There were six studies reporting associations between interpregnancy weight change and stillbirth (1,129,998 women);[28,32,41,43,67,68] four could be pooled for meta-analysis of weight gain[28,32,67,68] and three for weight loss.[32,67,68] There was a significantly increased odds of stillbirth and weight gain (OR 1.49 95% CI 1.29, 1.42, I^2=53.9%) (Fig S9a) and weight loss (OR 1.22 95% CI 1.05, 1.42, I^2=0%) (Fig S9b). Subgroup analysis identified that this was only significant for studies which reported the BMI reduction within a specified range and not for BMI reduction with no upper limit. Two studies included data that could be included in the BMI stratified meta-analysis for stillbirth and weight gain and weight loss (Figs S9c and S9d).[41,67] There was a significantly increased odds of stillbirth and weight gain for both BMI subgroups, with similar effect sizes (BMI<25 kg/m^2 OR 1.25, 95% CI 1.11, 1.41, I^2=0%; BMI>25 kg/m^2 OR 1.28, 95% CI 1.04, 1.58, I^2=25.9%) (Fig S9c). There was no significant difference in odds of stillbirth and weight loss for either BMI subgroup (Fig S9d).

Meta-analysis preterm:

There were 15 studies that reported associations between interpregnancy weight change and preterm delivery (1,016,240 women);[25,31,36,48,50,55,61,69-76] 10 were pooled for meta-analysis of weight gain[36,41,48,50,55,61,70,72,75,76] and nine for weight loss.[36,41,48,50,55,70,72,75,76] There was no significant association between interpregnancy BMI gain and preterm delivery in the overall

analysis (OR 0.95 95% CI 0.89, 1.02, I^2=64.5%), or any of the subgroups (Fig S10a). There was some evidence of an increase in preterm delivery and interpregnancy weight loss (OR 1.06 95% CI 1.00, 1.13, I^2=22.4%), although this only remained significant for the subgroup where BMI loss without an upper limit (Fig S10b). There were four studies that reported data which could be pooled in the BMI stratified meta-analysis for preterm delivery and interpregnancy weight gain and for weight loss.[36,41,70,76] There was only a significantly increased odds of preterm delivery and weight gain for BMI>25k/m^2 (OR 1.11, 95% CI 1.03, 1.20, I^2=28.2%), and for weight loss and BMI<25 kg/m^2 (OR 1.21, 95% CI 1.11, 1.32, I^2=25.1%) (Fig S10c and S10d).

Meta-analysis low Apgar score/hemorrhage:

There were two studies reporting low Apgar score (528,303 women) [32,77] and two reported hemorrhage (26,388 women);[32,50] all were included in the meta-analysis for interpregnancy weight gain and weight loss. There was a significantly increased odds of low Apgar score and interpregnancy weight gain (OR 1.24, 95% CI 1.13, 1.36, I^2=23.65%) (Fig S11a), but no significant association with weight loss (OR 0.89, 95% CI 0.78, 1.01, I^2=0%) (Fig S11b). There was also no significant association between maternal hemorrhage and interpregnancy weight gain (OR 1.12, 95% CI 0.93, 1.34, I^2=0%) (Fig S12a) or loss and (OR 1.18, 95% CI 0.89, 1.56, I^2=0%) (Fig S12b).

Meta-regression, publication bias and sensitivity analysis:

Heterogeneity was high for multiple meta-analyses; some of this was partially explained by subgroup analysis which reduced heterogeneity to within the moderate or low ranges. Meta-regression was carried out to explore the remaining high levels of heterogeneity observed. There was no significant change to residual heterogeneity (I^2) for weight gain and GDM or

preeclampsia (Tables S12a and S12h), or for weight loss and GDM, LGA or SGA (Tables S12b, S12d and S12e). However, there were variables that significantly contributed to heterogeneity for the remaining analyses. These were the time period that data were collected (LGA, caesarean delivery and hypertensive disorders of pregnancy), the geographical region of study (caesarean delivery, preeclampsia and hypertensive disorders of pregnancy), sample size (caesarean delivery and preeclampsia), and the study design being prospective or retrospective (caesarean delivery) (Tables S12f-i). Although the residual heterogeneity was significantly reduced in these analyses, it still remained high with the exception of weight loss and preeclampsia (Table S12i) where sample size explained almost all of the heterogeneity (I^2 reduced from 92.2% to 4.5%). We were not able to explore the extent to which differences in population characteristics or outcome definition contributed to the between study heterogeneity due to the lack of consistency in how these data were reported.

There was no evidence of publication bias for weight gain or loss and hypertensive disorders of pregnancy, preeclampsia, LGA, SGA, caesarean delivery, VBAC and stillbirth (Fig S3g-h, S4e-f, S5e-f, S6g-h, S7g-h, S8e-8f, S9g-h). There was no evidence of publication bias for weight gain and GDM or preterm delivery (Figs S2c, S10g), but there was for weight loss (Figs S2d, S10h).

The sensitivity analysis suggests that meta-analysis results were robust for most outcomes, with limited impact on the effect size or significance of pooled results for weight gain and loss and GDM, hypertensive disorders, preeclampsia, LGA, SGA, caesarean and VBAC (Figs S2a-b, S3e-f, S4c-d, S5c-d, S6e-f, S7e-f, S8c-d); weight gain and stillbirth and preterm delivery but not for weight loss (Figs S9e-f, S10e-f); and not for subgroup analysis for GDM and weight loss (Fig S2b).

Narrative synthesis:

The additional data for perinatal outcomes that could not be included in the meta-analysis due to data arising from a single study or the results from multiple studies not suitable for pooling, are reported in Table S13. Neonatal outcomes included NICU admission (n=280),[28] low birth weight (categorized according to sex-dependent z-scores, n=12,058),[58] preterm and recurrent preterm birth (dataset did not differentiate between the two outcomes; n=1,241),[71] recurrent preterm birth only (n=7,674),[69,73] hypoglycemia (n=1,048),[32] respiratory distress (n=1,048),[32] neonatal seizures (n=1,071),[77] meconium aspiration (n=757),[77] neonatal, postneonatal and infant mortality (n= 515,252),[67] infant anthropometrics (n=73),[45] perinatal death (n=24,795),[43] a composite measure of congenital anomalies (n=45,439),[26,43] spina bifida (n=5,060),[78] conotruncal heart defects (n=1,685),[79] gastroschisis (n=5,343)[80] and cleft lip (n= 220,328).[81] For neonatal outcomes, an interpregnancy gain or loss of ≥1 BMI unit appears to be associated with an increased risk for spina bifida,[78] gastroschisis,[80] and respiratory distress[32] compared to stable weight. No associations were found between preconception or interpregnancy weight loss or gain and the following labour and delivery outcomes: 4th degree perineal tears (n=2,860),[32] episiotomy (n=2,860),[32] shoulder dystocia (n=2,860),[32] instrumental delivery (1 study, n=23,329)[50], and caesarean delivery (n=73).[45] Placental weight (n=5,079)[50] was positively correlated with weight change, as women who gained or lost weight preconception or interpregnancy had heavier or lighter placentas respectively, than women who had stable weight. Maternal outcomes associated with an increased risk following weight gain were pregnancy loss (1 study, n=995),[82] maternal morbidity (1 study, unknown sample size)[61], GDM (n=73),[45] recurrent GDM (n=501),[44] and GWG (n=799).[83]

Discussion:

This systematic review and meta-analysis aimed to summarize the effect of preconception and interpregnancy weight change on perinatal health outcomes. The search yielded data pertaining to 34 outcomes. Meta-analysis identified evidence of a significantly increased risk of GDM, LGA, preeclampsia, and hypertensive disorders following preconception and interpregnancy weight gain, irrespective of preconception BMI. Interpregnancy weight gain also significantly increased the odds for caesarean delivery, low APGAR scores, stillbirth, and unsuccessful VBAC, regardless of prepregnancy BMI; there was a lack of data available for preconception weight gain and these outcomes. Interpregnancy weight loss significantly increased the risk for SGA and preterm delivery, however, these associations were not observed with preconception weight loss. When stratified by BMI, women with a BMI $\geq$ 25.0 kg/m^2 who gained weight between pregnancies had increased odds of hypertensive disorders, preterm birth and caesarean delivery. Women with a BMI $\leq$ 25.0 kg/m^2 who gained weight between pregnancies were at increased risk for GDM, hypertensive disorders, and caesarean delivery. When stratified by BMI, interpregnancy weight loss reduced the risk for GDM, hypertensive disorders, and caesarean delivery for women who had a BMI $\geq$ 25.0 kg/m^2. For women who had a BMI $\leq$ 25.0 kg/m^2, weight loss interpregnancy or preconception was associated with increased risk of SGA and reduced risk for LGA. Additionally, interpregnancy weight loss for women who had a BMI $\leq$ 25.0 kg/m^2 was associated with increased risk for preterm birth, and reduced risk for GDM. A narrative synthesis of data that could not be included in meta-analysis suggests that interpregnancy weight gain is associated with increased risk of maternal morbidity, pregnancy loss, neonatal seizures and meconium aspirations.

This review adds novel data building on the work of three previous systematic reviews that assessed only interpregnancy weight change and perinatal outcomes.[10-12] Our synthesis has incorporated results from an additional 30 studies which were not included in previous reviews and data for 34 outcomes, of which 26 have not been previously reviewed. Notably, the results of this review are relevant to women of all parities. We also performed subgroup analysis and meta-regression to explore heterogeneity, which is a novel contribution to the field, although there were some *a priori* factors that we were not able to explore. In line with previous findings,[10-12] this review identified an increased odds for GDM, hypertensive disorders, preeclampsia, LGA, and caesarean delivery following interpregnancy weight gain. Our findings extend current data and suggest that preconception weight gain also increases the odds of women developing GDM and preeclampsia. Additionally, our findings add that interpregnancy weight loss can increase the risk for SGA and preterm delivery. Collectively, these results highlight the need for effective preconception and interpregnancy weight management support regardless of women's parity.

Limited studies have investigated the consequences of preconception weight change compared with interpregnancy. A recent scoping review that aimed to summarize obesity prevention behavioral interventions for women of childbearing age identified that most studies have only targeted postpartum weight management, and therefore nulliparous women are not included.[84] We most often see the inclusion of nulliparous women in infertility weight-management interventions.[85,86] However, women who are not seeking fertility treatment may also require weight management support. Although an exact prevalence for weight loss attempts prior to pregnancy is not available, more than 40% of adults try weight management annually comprising primarily of women.[16] From these statistics we can infer that preconception weight support should not be reserved only for women seeking fertility care.

Additionally, no studies reported maternal mental health outcomes. Poor preconception mental health is associated with perinatal complications such as low birthweight, hypertensive disorders, high blood sugar, and premature labour.[87] Furthermore, prenatal depression is positively correlated with maternal BMI, positioning women with obesity at the highest risk for detrimental mental health outcomes during pregnancy.[88] The desire to lose weight among women is also associated with suboptimal mental health.[89] Specifically, data from non-pregnant women undergoing weight loss interventions suggests a negative correlation between self-perceived control over their weight and deleterious psychological variables like shame and self-criticism.[90] It may be that women experiencing preconception weight change, whether intentional or not, can also be at an increased risk for poor prenatal mental health outcomes, and this warrants further investigation.

Studies have shown that preconception obesity is a risk factor for perinatal complications,[1,2] and accordingly, maternal obesity guidelines suggest weight loss before conception to improve health outcomes.[5-7] In our review, sub-analyses were performed considering prepregnancy BMI. Women with an elevated BMI who gained weight between pregnancies had an increased odds of hypertensive disorders and caesarean deliveries in subsequent pregnancies, whereas weight loss between pregnancies reduced the odds of GDM, hypertensive disorders, and caesarean deliveries. Of note, we could not assess the relationship between these outcomes and preconception weight loss. Furthermore, irrespective of BMI, there was an increased risk for SGA (interpregnancy) and preterm loss (preconception and interpregnancy) with weight loss. Unfortunately, due to limited data on preconception weight loss, high heterogeneity, and variable methods of measuring weight loss before pregnancy, a recommendation for an amount of weight that women should aim to lose in a given timeframe to

improve outcomes cannot be confirmed. Lastly, all analyses were compared to stable weight as the reference (i.e., no change or no more than 1 BMI unit change) before pregnancy. Perhaps these findings may suggest that instead of recommending weight loss, we should consider highlighting the importance of improving health behaviors to establish a stable preconception weight.

Strengths of this review include the rigorous search strategy, including supplementary searches that involved hand searches of reference and citation lists. All screening, data extraction, and quality assessment were carried out by two independent investigators. In addition, included studies were of medium to high quality. To our knowledge, this is the first meta-analysis that has incorporated preconception weight change, and therefore findings apply to women of any parity. The results from our review are limited by the few studies that evaluated preconception weight change in comparison to interpregnancy, and none that exclusively included nulliparous women. Sources of heterogeneity between studies that were not explored due to lack of data may also have influenced findings, such as maternal ethnicity, behavioural factors (e.g., diet, physical activity, smoking), socioeconomic status, and women with prenatal complications; although some studies did adjust for these variables or excluded women with pre-existing complications from their analysis.

Conclusion:

Our systematic review and meta-analysis showed an increased risk for perinatal complications following preconception or interpregnancy weight instability. Regardless of prepregnancy BMI, women who gain weight preconception or between pregnancies have an increased odds of GDM, hypertensive disorders, preeclampsia, and LGA. Additionally, weight

loss between pregnancies increases the risk for SGA, while interpregnancy or preconception weight loss can increase the risk for preterm birth. Further studies are needed explicitly evaluating the preconception period, and the impact of weight change on maternal mental health outcomes. This review emphasizes the need for effective preconception and interpregnancy weight management support to prevent perinatal complications.

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