BMJ Open

Interpregnancy Weight Change and Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018778
Article Type:	Research
Date Submitted by the Author:	20-Jul-2017
Complete List of Authors:	Oteng-Ntim, Eugene ; London School of Hygiene and Tropical Medicine Mononen, Sofia; King's College, London, Division of Reproduction and Endocrinology, Maternal and Fetal Research Unit, 10th Floor North Wing, St Thomas Hospital, SE1 7EH Sawicki, Olga; London School of Hygiene and Tropical Medicine Seed, Paul; Kings College, London, Division of Reproduction and Endocrinology, Maternal and Fetal Research Unit, 10th Floor North Wing, St Thomas Hospital, SE1 7EH Bick, Debra; Kings College London, Florence Nightingale School of Nursing and Midwifery Poston, Lucilla; Kings College, London, Division of Reproduction and Endocrinology
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	body mass index, interpregnancy, obesity, pregnancy

Interpregnancy Weight Change and Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis

Eugene Oteng-Ntim, Sofia Mononen, Olga Sawicki, Paul Seed, Debra Bick, Lucilla Poston

London School of Hygiene and Tropical Medicine, London, UK

Eugene Oteng-Ntim PhD
Associate Professor Epidemiology and Population Health
Consultant Obstetrician,

Olga Sawicki MD, MSc
Senior Scientist in UNAIDS

Division of Women's Health, King's College London, St. Thomas' Hospital, London, UK

Sofia Mononen
MBBS BSc student

Paul Seed MSc
Senior Lecturer in Medical Statistics

Prof Debra Bick PhD
Professor of Evidence Based Midwifery

Prof Lucilla Poston PhD
Tommy's Campaign Professor of Maternal and Fetal Health, Head of Division of Women's Health

Correspondence to: Dr Eugene Oteng-Ntim, Department of Women's Health, Guy's and St Thomas' National Health Service Foundation Trust, London SE1 7EH, UK, eugene.oteng-ntim@gstt.nhs.uk

ABSTRACT

Objectives: To evaluate the effect of interpregnancy BMI change on pregnancy outcomes, including large-for-gestational-age babies (LGA), macrosomia, gestational diabetes mellitus (GDM), and caesarean section.

Design: Systematic review and meta-analysis of population-based cohort studies with the study protocol registered a priori.

Data sources: Literature searches were performed across Cochrane, MEDLINE, EMBASE, CINAHL, Global Health and MIDIRS databases.

Study selection: Population-based cohort studies were included with participants between parity 0 to 1 with no history of diabetes mellitus.

Main outcome measures: Adjusted odds ratios (aOR) with 95% confidence intervals were used to evaluate the association between interpregnancy BMI change on five pregnancy outcomes.

Results: A total of 910,951 women with singleton births from parity 0 to 1 were enrolled in the meta-analysis of ten observational studies selected from 924 identified studies. In all women irrespective of BMI at first pregnancy, a substantial increase in interpregnancy BMI (> 3 BMI units) was associated with an increased risk of LGA (aOR=1.85, 95% CI 1.71-2.00, p=0.000), GDM (aOR=2.28, 1.97-2.63, p=0.000), macrosomia (aOR=1.537, 95% CI 0.939-2.505) and c-section (aOR=1.62, 1.22-2.15, p=0.001) compared with the reference category. An interpregnancy BMI decrease was associated with a decreased risk of LGA births (aOR=0.67 95% CI 0.54-0.84,p=0.000), macrosomia (aOR=0.5 95% CI 0.35-0.71), and GDM (aOR=0.78 95% CI 0.67-0.92, p=0.002). Women with a normal BMI (<25) at first pregnancy who have a substantial increase in BMI (> 3 units) between pregnancies were at a higher risk of LGA (aOR=2.10, 1.93-2.29) and GDM (aOR=3.10, 2.74-3.50) when compared to a reference than women with a BMI ≥ 25 at first pregnancy.

Conclusions: Women who gain weight between pregnancies are at higher risk of developing GDM, CS and LGA babies in the subsequent pregnancy. Women who lose weight between pregnancies have a lower risk of GDM and LGA babies. Clinicians should aim to address weight change after birth of the first child in order to lower risk of adverse pregnancy outcomes.

Registration: PROSPERO CRD4201604

Strengths and limitations of the study

- We believe this to be the first meta-analysis completed on the topic of interpregnancy weight change and its effect on four adverse pregnancy outcomes.
- A large sample size of 910,951 women was collected from ten well-adjusted population-based observational studies, with two methods used to assess the quality of the studies.
- Sensitivity analysis was conducted to remove low quality research, which did not change the direction of effect for any outcome.
- Limitations included limited generalisability, as the research was conducted in high-income countries in women between parity 0 to 1. Further, additional confounding factors (such as breastfeeding) could affect the results.

INTRODUCTION

The associations between high pregravid body mass index (BMI) and maternal and neonatal complications are well established;[1] complications include gestational diabetes mellitus (GDM), caesarean section (CS), preeclampsia, macrosomia, prematurity, and stillbirth.[2] These outcomes are of public health importance because they add to the disease burden of women and their infants thereby increasing health care costs.[3] Mirroring the trend of the global obesity epidemic (more than half of all women of reproductive age in the UK are overweight or obese),[4] the prevalence of all these pregnancy complications has risen, as has the focus on maternal weight management as a means to improve the health of women and their children.

Previous studies have investigated the effect and impact of increased weight on adverse outcomes at all stages of the periconceptional period.[5] Lifestyle and medical interventions during pregnancy have shown little effect on pregnancy outcomes.[6] In the meantime, interpregnancy care is aimed at optimising outcomes of women and their future babies.[7] But standards are lacking[8] and, owing to the paucity of literature, systematic reviews and meta-analysis, any effect of interpregnancy care on pregnancy outcomes remains nascent.[8-10]

Despite a plausible rationale for weight management as part of interpregnancy planning, a knowledge gap exists amongst healthcare providers and women of reproductive age of the impact of weight change between pregnancies. Interpregnancy weight change is defined as the difference in BMI between one and the next pregnancy recorded at the first antenatal visit.[11] Whilst the number of relevant studies has expanded in recent years,[16-25] no meta-analysis has been attempted. The aim of this meta-analysis was to address this gap by examining the association between interpregnancy weight change and the most prevalent associated adverse pregnancy outcomes: GDM, CS and large birth weight babies in the next pregnancy (see table 1 for definitions). Where possible, the data were divided according to maternal BMI <25 kg/m^2 and BMI ≥25 kg/m^2, in order to address effects of intepregnancy weight change in the overweight/obese population compared to women with a normal BMI. Only the first two successive pregnancies were assessed in order to minimise confounding due to any effects of parity on pregnancy outcome.

Table 1: **Definitions of maternal and foetal outcomes used throughout this review**

Outcome	*Definition*
Large for gestational age (LGA)	A baby with birth weight ≥90th percentile of all babies with same gestational age[2]
Macrosomia	Birth weight of >4000g[12]
Caesarean section	Surgical incision into abdominal and uterine wall to achieve delivery of the baby[13]
Gestational diabetes mellitus (GDM)	Any degree of glucose intolerance with onset or first recognition during pregnancy[14]

METHODS

Protocol and registration

The study was registered in PROSPERO International prospective register of systematic reviews (CRD42016041299). The criteria outlined in the PRISMA statement and the MOOSE checklist was adhered to.

Information sources

Electronic databases including CINAHL, EMBASE, MEDLINE, the Cochrane Database of Systematic Reviews, MIDIRS and Global Health were searched from January 1990 to January 2017. Searches were limited to studies in humans. There were no language constraints. In addition, references from bibliographies and citations were manually searched. A grey literature search was run until January 1, 2017 across the following clinical trials registries: TRIP Database, EThOS, WHO International Clinical Trials Registry Platform Search Portal and the EU Clinical Trials Register.

Table 2: Search strategy for MEDLINE

1	exp birth intervals/
2	(interpregnan* or inter-pregnan* or (birth adj interval) or (between adj pregnan*) or (successive adj pregnan*) or interbirth or (pregnan* adj spacing) or (pregnan* adj interval) or (birth adj spacing) or interdelivery or (consecutive adj pregnan*) or (following adj pregnanc*) or (subsequent adj pregnan*)).mp.
3	1 or 2
4	((body adj weight) or body mass index or BMI or (weight adj change) or (weight adj los*) or (weight adj decrease) or (weight adj gain*) or (weight adj increase) or (BMI adj change) or (body adj mass adj index) or (body adj weight adj change)).mp.
5	((pregnancy adj complication) or (f?etal adj outcome) or (pregnancy adj outcome) or (adverse adj outcome) or macrosomia or large for gestational age or LGA or large-for-gestational-age or (birth adj weight) or GDM or (gestational adj diabetes) or c-section or (c?esarian adj section).mp.
6	3 and 4 and 5
7	Limit 6 to humans

Search strategy

A search strategy was developed for MEDLINE (see table 2) and adapted for other databases. The following combination of MeSH terms and free text were used: interpregnancy, prepregnancy, weight gain, weight loss, neonatal outcomes, and pregnancy complications. The full search and data extraction was performed by two independent investigators (SM and OS).

Outcome measures

Four of the most prevalent adverse outcomes were chosen as outcomes of interest for this review. These included LGA, macrosomia, c-section (CS) and GDM (defined in table 1). It should be noted that throughout this paper, BMI will be referred to in groups according to the WHO and NICE BMI classifications.[15]

Study selection

Observational studies such as cohort and case-control studies were included, with studies limited to humans. Only singleton births from parity 0 to 1 were included. Studies that included women with previous diabetes diagnoses were excluded, as were studies published as conference abstracts, reviews, pharmacological or surgical interventions for weight loss, case reports or unpublished trials. Citations found through database searches and other searches such as browsing bibliographies were combined and duplicates excluded.

Data collection and extraction

The Cochrane Good Practice Data Extraction Form was used for extracting relevant data of each study. Raw data was collected where available or calculated from the information given. Adjusted odds ratios and confidence intervals were extracted from all papers. Additional information collected from studies included: first author's name and year of publication, study design, setting, study period, sample size, outcomes, inclusion/exclusion criteria, quality assessment and population demographics and factors that each study adjusted for (including age, race, socioeconomic status, interpregnancy interval, previous maternal disease, gestational weight gain and education level).

To study whether association between change in body weight and adverse outcomes differed, study groups were classified as "large increase in BMI", "moderate increase in BMI" and "decrease in BMI". These groups were defined as BMI increase of more than 3 units (large increase), BMI increase between 1 and 3 units (moderate increase) and BMI decrease more than 1 units (decrease). If an outcome had small number of studies, substantial increase and moderate increase were combined as "increase in BMI". Interpregnancy weight change was defined as the prepregnancy BMI before first pregnancy to the prepregnancy BMI before second pregnancy. Where possible, data was divided into subgroups based on maternal BMI before first pregnancy (<25 kg/m^2 and ≥ 25 kg/m^2) in order to assess the effect of BMI change from a normal BMI compared with women who were

overweight or obese. For each outcome, the effect of BMI change on adverse pregnancy outcome was compared to the reference category, which was defined as women who maintained BMI between pregnancies or had a BMI change between -1 to 1 units.

Two investigators (SM, OS) independently performed the literature search, assessed the eligibility and quality of the retrieved papers, and performed the data extraction. The two authors compared the results and disagreements were resolved by a third reviewer (EO).

Risk of bias assessment

To assess the quality of the studies, a modified Newcastle-Ottawa scale and a Cochrane analysis of bias were performed. Sensitivity analysis was performed by removing studies with a NOS score (≤4 stars) or a high level of bias (<3 points) according to the Cochrane analysis.

Statistical analysis

Forest plots were made for each outcome to assess overall effect size and heterogeneity using Stata SE 14 (StataCorp, College Station, Texas, USA). Random effects model was used to account for variability across studies. Study weight was calculated using the inverse variance method. Data was pooled and heterogeneity assessed with the I^2 statistic, with a high heterogeneity defined as being over 50%. Results were considered statistically significant if p was less than 0.05. Sensitivity analysis was performed by removing low quality studies. Analysis was then repeated and results compared.

Role of funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Patient Involvement

No patients were involved in setting the research question or the outcome measures, and no patients were involved in developing plans for design or implementation of the study. Further, no patients were asked to advice on interpretation or writing up of results. Since this meta-analysis used aggregated data from previous trials, it is unable to disseminate the results of the research to study participants directly.

RESULTS

Literature search results

Results from the literature search came back with ten studies to be included in the qualitative synthesis. The 2009 PRISMA flow diagram can be seen in figure 1, showing the process of study selection.

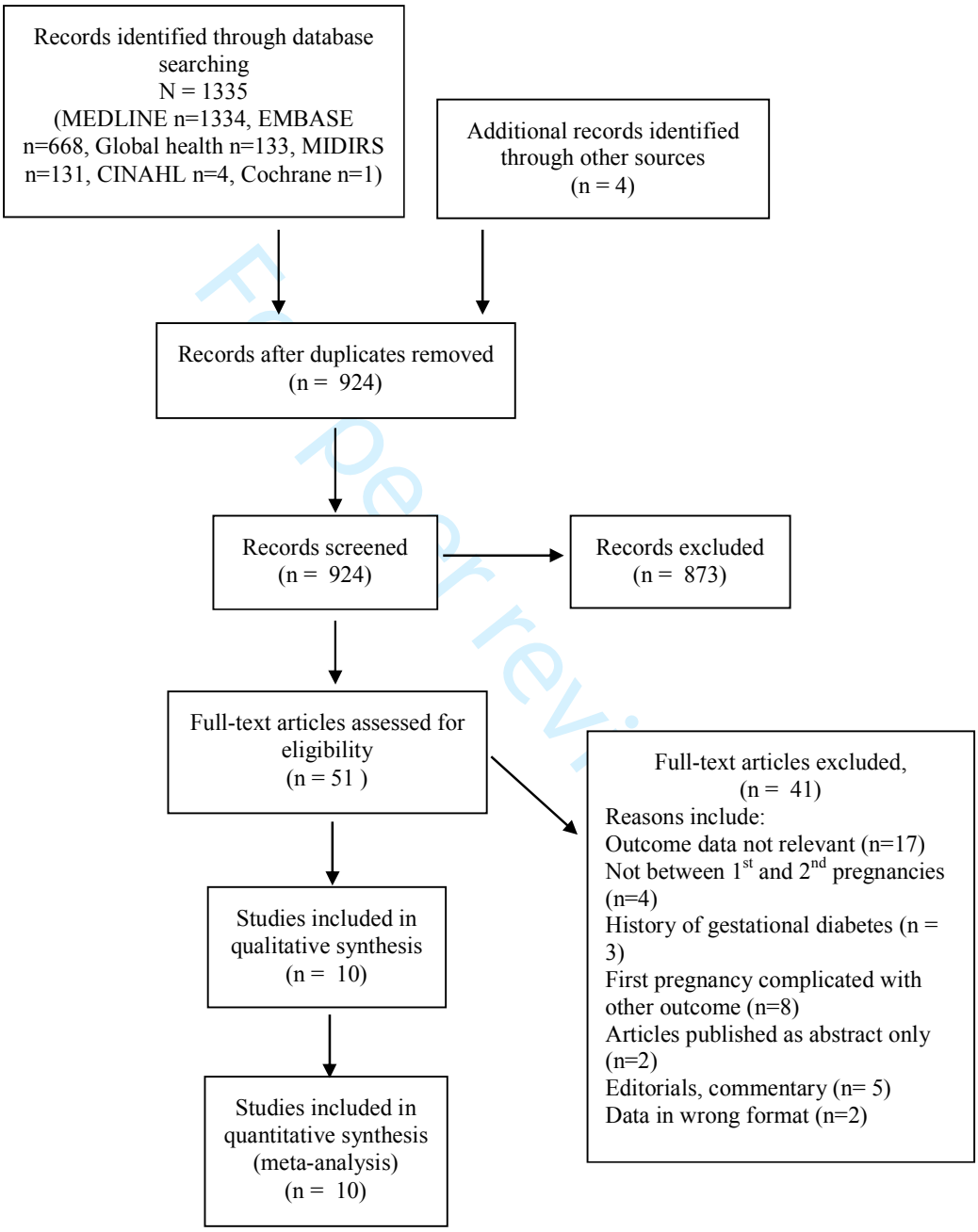

Figure 1: 2009 PRISMA flow diagram showing results of literature search

Study characteristics

Study characteristics can be found in table 3. Out of the studies, six were from USA[16,17,18,19,20,21], two from Scotland[22,23], one from Sweden[24], and one from Belgium[25]. Four papers studied GDM, five papers studied LGA, one paper studied macrosomia, and six papers studied c-section (table 3). All studies presented their data in adjusted odds ratios (aOR). Six out of the ten studies used self-reports to record prepregnancy weight and height. All studies adjusted for confounding variables such as age, race, education and marital status with most studies also adjusting for interpregnancy interval, smoking, socioeconomic status, alcohol use, country of birth and

maternal illness. About half of the prospective studies were community-based, using data found from national or state databases whilst other studies used hospital data.

Data quality

Data quality was assessed using a modified Newcastle-Ottawa scale[26] as well as a Cochrane tool of assessing bias in studies[27]. The results of this data quality assessment can be seen in appendix 1, tables 6 and 7. The exposed cohort was defined as women with a change in interpregnancy BMI, whilst the non-exposed cohort was defined as women who maintained BMI or their BMI changed between -1 and 1 units. The criteria for allocating stars (out of a total of seven stars) awarded to each study according to this NOS criteria can be found in appendix 1 table 5. Despite authors attempting to adjust for the missing data, only five studies assessed the problem of missing data and analysed if this missing data was significant. One study[25] did not report data unless it was statistically significant, giving rise to a possible high risk of reporting bias. Self-reported assessment of exposure as well as incomplete data are the two greatest sources of bias in the studies. The total score shown in appendix 1, table 7 allows for comparison of Cochrane analysis of bias and NOS. These two assessments show good agreement; good quality studies tended to have a lower risk of bias.

Table 3: Study characteristics of studies chosen for meta-analysis and review of inter-pregnancy weight change and adverse pregnancy outcomes

Study ID	Study date	Sample size	Study setting	Study type	Relevant outcomes	BMI change measured in	Confounders adjusted for	Self-reported weight/ height	Limitations
Bogaerts[25]	2013	7,897	Belgium	Population-based retrospective cohort	GDM, c-section, macrosomia	Units (-1, -1 to 1, 2, >2, >3)	Age, marital status, alcohol use, inter-pregnancy interval and gestational weight gain	Yes	No information on prior diabetes, hypertension, smoking, education or ethnicity, small sample. Non-significant data excluded.
Ehrlich[16]	2011	22,351	USA	Population-based retrospective cohort	GDM	Units (>-2, -1 to -2, 0-1, 1-1.9)	Pre-pregnancy BMI, age, race, place of birth, GDM in 1st pregnancy, inter-pregnancy interval	No	No information on gestational weight gain, physical activity, diet, breastfeeding
Getahun[17]	2007a	146,227	USA	Population-based retrospective cohort	LGA	Groups (underweight, normal, overweight, obese)	Age, race, education, marital status, inter-pregnancy interval, smoking, alcohol	Yes	No information on genetics factors, diet, physical activity or stress
Getahun[18]	2007b	113,789	USA	Population-based retrospective cohort	C-section	Groups (underweight, normal, overweight, obese)	Age, race, education, marital status, inter-pregnancy interval, smoking, alcohol, previous c-section	Yes	No information on genetics factors, diet, physical activity or stress
Jain[19]	2013	10,444	USA	Population-based retrospective cohort	LGA	Weight loss/weight gain	Pre-pregnancy BMI, age, race, ethnicity, marital status, socioeconomic status, education, inter-pregnancy interval	Yes	No information on genetic factors, diet, physical activity or stress
Villamor[24]	2006	207,534	Sweden	Population-based prospective cohort	GDM, LGA, c-section,	Units (<-1, -1 to 1, 1 to <2, 2 to <3, >3)	Age, smoking, pre-pregnancy BMI, country of origin, education, inter-pregnancy interval, complications of first pregnancy	No	No information for genetic factors, diet, physical activity or stress.

Study ID	Study date	Sample size	Study setting	Study type	Relevant outcomes	BMI change measured in	Confounders adjusted for	Self-reported weight/ height	Limitations
Wallace[22]	2014	24,520	Scotland	Population-based retrospective cohort	LGA, c-section	Units (<-1, -1 to 1, 1 to <2, 2 to <3, >3)	Age, smoking, inter-pregnancy interval, complications of first pregnancy	No	Low ethnic diversity, low event rate, no information for genetic factors, diet, physical activity or stress
Wallace[23]	2016	12,740	Scotland	Population-based retrospective cohort	LGA, c-section	Units (<-1, -1 to 1, 1 to <2, 2 to <3, >3)	Age, smoking, inter-pregnancy interval, complications of first pregnancy	No	Low ethnic diversity, low event rate, no information for genetic factors, diet, physical activity or stress, maternal weight late in pregnancy not measured
Whiteman[20]	2011a	100,828	USA	Population-based retrospective cohort	C-section	Groups (underweight, normal, overweight, obese)	Age, race, education, marital status, smoking, alcohol use, inter-pregnancy interval	Yes	Use of vital statistics data, no information for genetic factors, diet, physical activity or stress
Whiteman[21]	2011b	232,272	USA	Population-based retrospective cohort	GDM	Groups (underweight, normal, overweight, obese)	Age, race, education, marital status, smoking, alcohol use, inter-pregnancy interval	Yes	Inability to separate GDM from type 2 diabetes, no information for genetic factors, diet, physical activity or stress

Outcomes

A decrease in BMI (>1 BMI unit) was associated with a 33% reduction in LGA births irrespective of BMI at the beginning of the first pregnancy (aOR 0.67 (95% CI 0.54-0.84), I^2=79.4%), whilst a moderate increase in BMI is associated with a 44% higher risk of LGA birth compared with the reference category (aOR 1.44 (95% CI 1.33-1.57), I^2=36.4%). A significant increase in BMI, defined as being an increase of over 3 units, had the highest risk of LGA birth (aOR=1.85 (95% CI 1.71-2.00), I^2=0%) (figure 2). Z-values and p-values for these results (appendix 3) show that all three pooled estimates were statistically significant (p=0.000).

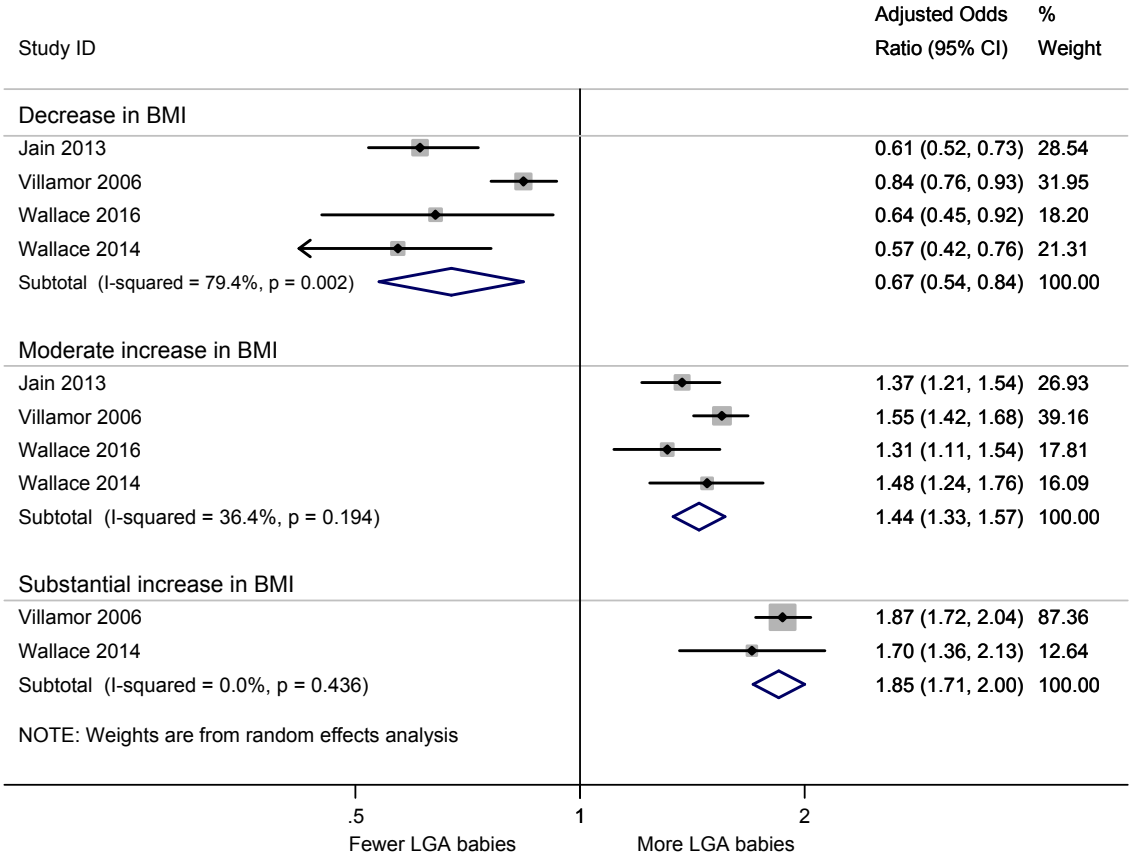

Figure 2: Forest plot showing change in interpregnancy weight compared with reference category and the risk of large for gestational age births in the subsequent pregnancy, irrespective of BMI at the beginning of the first pregnancy. (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

Only one study included macrosomia as an outcome[25]. Their results showed that decrease in BMI had a reduced risk of macrosomia, aOR=0.5 (0.35-0.71), with a substantial increase in BMI associated with a higher risk of macrosomia (aOR=1.537(0.939-2.505).

A decrease in BMI (>1 BMI unit) resulted in a decreased risk of GDM irrespective of BMI at the beginning of the first pregnancy (aOR 0.78 (95% CI 0.67-0.92), I^2=35.6%). A moderate increase in BMI was associated with a 56% increased risk of GDM (aOR 1.56 (95% CI 1.35-1.80), I^2=54.8%). A substantial increase in BMI (more than 3 units) was similarly associated with a high risk of GDM (aOR 2.28 (95% CI 1.97-2.63), I^2=0.0%) (figure 3). P-values for these pooled results were statistically significant for decrease (p=0.002) moderate (p=0.000) and substantial increase in BMI (p=0.000) and risk of GDM (appendix 3).

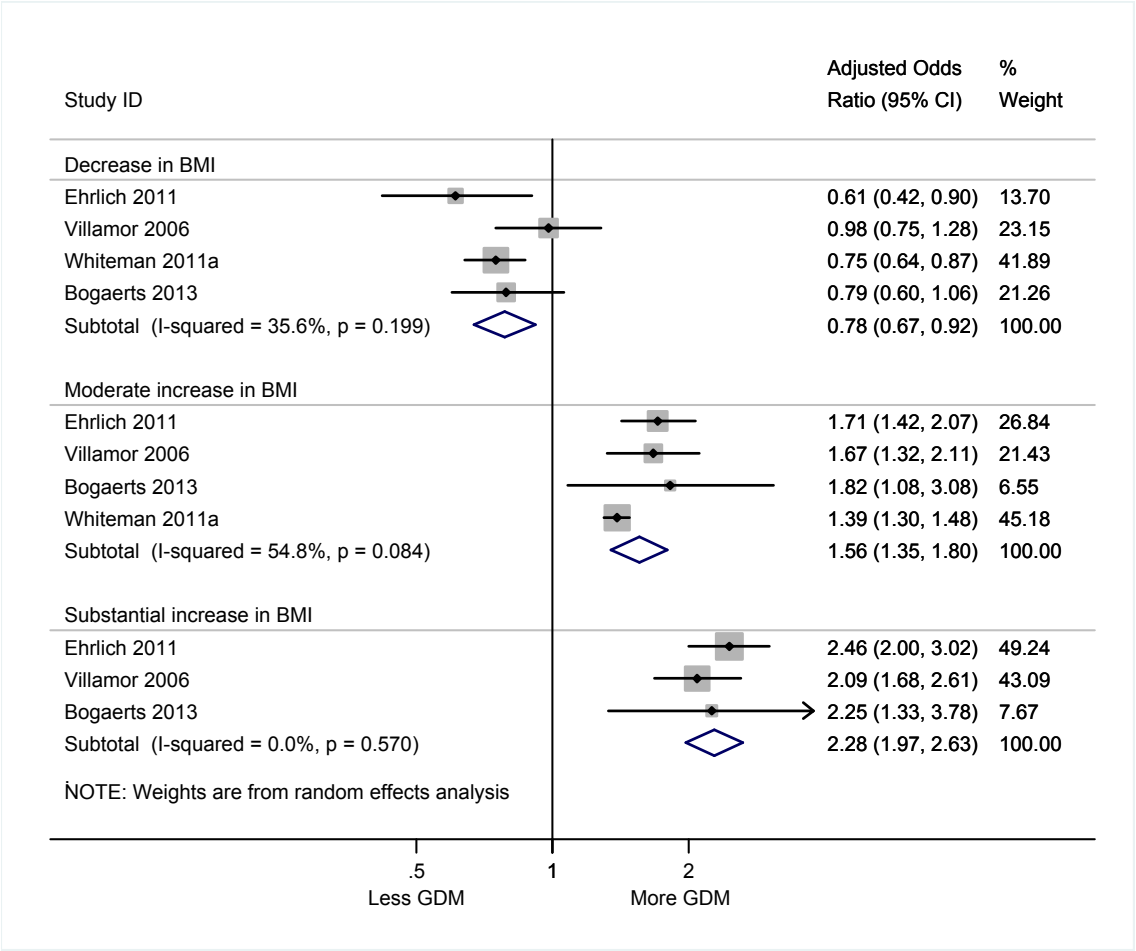

Figure 3: Forest plot showing change in interpregnancy weight compared with reference category and the risk of gestational diabetes mellitus in the subsequent pregnancy, irrespective of BMI at the beginning of the first pregnancy. (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

A decrease in BMI (decrease of more than one BMI unit) resulted in a slightly increased risk of c-section births irrespective of BMI at the beginning of the first pregnancy (aOR 1.05 (95% CI 0.89-1.23), I^2=43.0%), though this was not statistically significant (p=0.579, appendix 3), whilst a moderate increase and substantial increase in BMI were associated with higher risks of c-section (aOR 1.22 (95% CI 1.06-1.44) I^2=77.2%) and aOR 1.62 (1.22-2.15) I^2=76.9%), respectively) (figure 4). Both moderate and substantial increase in BMI were statistically significant (p=0.006 and p=0.001, respectively) (appendix 3).

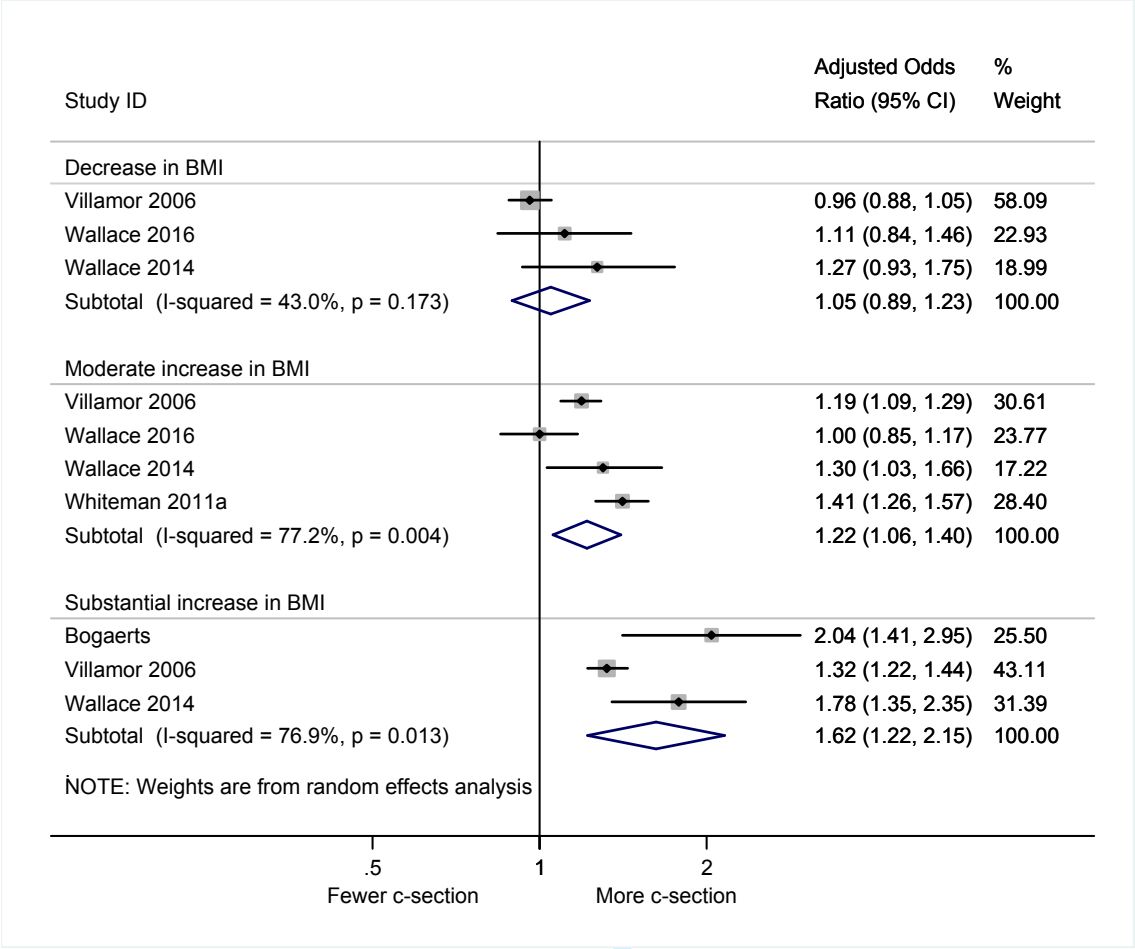

Figure 4: **Forest plot showing change in interpregnancy weight with reference category and the risk of c-section in the subsequent pregnancy irrespective of BMI at the beginning of the first pregnancy. (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)**

Outcomes grouped by BMI before first pregnancy

Some studies divided women into women with a BMI of less than 25 at their first pregnancy (normal) and women with a BMI over 25 at their first pregnancy (overweight/obese).

Women of normal BMI (<25) at beginning of first pregnancy are at a higher risk of LGA babies if they have a substantial increase of BMI (OR 2.10 (95% CI 1.93-2.29), I^2=7.7%) compared with women who had an overweight/obese BMI (≥25) at the beginning of first pregnancy (OR 1.69 (95% CI 1.37-2.09), I^2=86.2%). The same trend is apparent in a moderate increase of BMI (an increase of between 1 and 3 units) (refer to appendix 2 fig 5 and 6).

Women of normal BMI (<25) at beginning of first pregnancy are at a higher risk of GDM if they have a substantial increase of BMI (OR 3.10 (95% CI 2.74-3.50), I^2=0.0%) compared with women who had an overweight/obese BMI (≥ 25) at the beginning of first pregnancy (OR 1.82 (95% CI 1.34-2.48), I^2=51.6%) (appendix 2 fig 7 and 8). The same trend is apparent in a moderate increase of BMI.

Women of normal BMI (<25) at beginning of first pregnancy are at a higher risk of c-section if they have a substantial increase of BMI (OR 1.70 (95% CI 1.34-2.16), I^2=87.7%) compared with women who had an overweight/obese BMI (≥ 25) at the beginning of first pregnancy (OR 1.52 (95% CI 0.84-2.75), I^2=78.0%) (appendix 2 fig 9 and 10). The same trend is apparent in a moderate increase of BMI. However, the confidence intervals of these two odds ratios overlap and therefore the statistical significance can be questioned.

Sensitivity analysis

Sensitivity analysis was assessed by removing studies that had a high level of bias (<3 on the Cochrane analysis of bias) or were of low quality according to the Newcastle-Ottawa scale (≤4 stars). Removal of low quality studies did not change the significance of results and the direction of effect remained the same. For LGA in women with a BMI < 25 (appendix 4), results before removal of studies included decrease in BMI (aOR 0.66 (0.51-0.85), I^2=70%), moderate increase in BMI (aOR 1.62 (1.54-1.71), I^2=0%) and substantial increase (aOR 2.10 (1.93-2.29), I^2=7.7%). After sensitivity analysis, heterogeneity for each of these groups decreased.

Heterogeneity

Generally, an I^2 value of 25% is considered low, 50% moderate and 75% high.[28] This value is thought to reflect the extent to which confidence intervals overlap with each other. When pooling results from population-based observational studies and the type of research used in this paper, it is impossible to control all possible confounders which is why a certain level of heterogeneity could be expected. As Higgins (2008) comments, if the predefined eligibility criteria and data are correct, any level of heterogeneity is acceptable, given that the authors can analyse the heterogeneous studies appropriately.[29] Analysis in this paper included random-effects analysis and sensitivity analysis. Further analysis of heterogeneity in this review is warranted; however, the Cochrane handbook recommends that meta-regression should not be completed if there are fewer than ten studies in a meta-analysis.[30] Further, it has been stated that this corresponds to ten studies for each covariate in meta-regression.[31] Due to this, the sources of heterogeneity will instead be discussed in limitations.

DISCUSSION

Major findings

This study found that in all women irrespective of BMI at first pregnancy, an interpregnancy BMI decrease is associated with a reduced risk of LGA births (aOR 0.67 (95% CI 0.54-0.84) p=0.000), reduced risk of macrosomia (aOR 0.5 (95% CI 0.35-0.71) and GDM (aOR 0.78 (95% CI 0.67-0.92) p=0.003) compared with reference category of women who retained BMI. A substantial increase in interpregnancy BMI (> 3 BMI units) is associated with an increased risk of LGA (aOR 1.85 (95% CI 1.71-2.00) p=0.000), GDM (aOR 2.28 (95% CI 1.97-2.63) p=0.000), c-section (aOR 1.62 (95% CI 1.22-2.15) p=0.001) and macrosomia (aOR 1.54 (95% CI 0.94-2.50) compared with the reference category (no weight change). Results did not change after sensitivity analyses removing low quality and studies with high bias. We believe this is the first systematic review and meta-analysis completed on the topic of interpregnancy weight change and adverse pregnancy outcomes in women from parity 0 to 1. When results are further analysed according to prepregnancy BMI (<25 or over 25 kg/m^2), women with a normal prepregnancy BMI at first pregnancy are at higher risk of LGA (aOR 2.10 (95% CI 1.93-2.29)) and GDM (aOR 3.10 (95% CI 2.74-3.50)) compared with women with a BMI ≥25.

Interpretation of major findings

It is known that obesity is the most common risk factor for insulin insensitivity.[32] A possible biological relation between obesity and adverse perinatal outcomes is the role of glucose and insulin insensitivity in pregnancy. The Pedersen Hypothesis, first suggested in 1952, stipulates that a higher-than-normal level of glucose (the main energy substrate of the foetus) transferred via the placenta to the foetus stimulates the release of insulin and insulin-like growth factors in the foetus, causing large for gestational age infants or macrosomic births.[33] This has been supported by research showing that high postprandial glucose concentration predicts large birth weight and hypoglycaemia is associated with growth restriction.[34]

An overweight or obese pregnant woman has a 50-60% increase in insulin insensitivity compared with a normal weighted pregnant woman.[35] Associated hyperglycaemia for the infant, as well as an increase in the release of free fatty acids and triglycerides from adipose stores have been studied to be associated with increased birth weight and adiposity of the offspring.[36] The reduction in insulin sensitivity as a result of interpregnancy weight gain may lead to higher levels of GDM, LGA, macrosomia and subsequent caesarean sections. On the contrary, weight loss and its association with increased insulin sensitivity may therefore result in reduced numbers of GDM and large babies. Studies have found that not all interpregnancy weight gain is attributed to weight gain in pregnancy: 0.45 kg can be credited to the trend of weight gain over time.[37] Research has also shown that women with a BMI ≥25 before pregnancy experience greater increases in postpartum body weight, and weight change 12 months postpartum is largely influenced by the prepregnancy body weight.[38] Interpregnancy weight gain as a result of both insufficient gestational weight loss after the previous pregnancy, combined with the normal trend of weight gain over time may have an additive or synergistic effect and result in further lowering of insulin sensitivity.

Strengths

We believe this is the first systematic review and meta-analysis completed on the topic of interpregnancy weight change and adverse pregnancy outcomes in women from parity 0 to 1 with singleton births. This review synthesised the available evidence on the effect of interpregnancy weight change, defined as the difference in BMI in early pregnancy between successive pregnancies, on major complications. The findings of ten cohort studies showed that interpregnancy weight gain was strongly associated with an increased risk of namely, GDM, CS, and large birth weight babies among all women regardless of initial BMI status. Conversely, interpregnancy weight loss was strongly associated with a reduced risk of GDM, and large birth weight in the second-born offspring but had no detectable effect on the rate of CS. The criteria outlined in the PRISMA statement and the Cochrane Handbook for Systematic Reviews of Intervention was adhered to, and this can be seen in appendix 5. Furthermore, the MOOSE checklist of recommendations for reporting meta-analyses of observational studies was followed. Results did not change even after sensitivity analyses of high methodological quality studies.

Studies included in this review were cohort studies with generally large sample sizes, resulting in a large pooled sample of almost one million women. The strengths of using these studies meant that they are population-based, with a generally representative population. Outcomes were classified in the same way in each study and for most of the outcomes it is objectively defined to classify if the outcome occurred or not, reducing a possible bias of assessment of outcome. In addition to this, the reliability of medical records has shown good level of both inter-rater and intra-rater reliability.[39] This review used two different ways of analysing the quality of studies and possible sources of bias – the Newcastle-Ottawa scale and the Cochrane analysis of bias. All studies had at least four stars on the NOS, and sensitivity analysis was performed to remove low quality studies or studies with a high bias. All studies used adjusted odds ratios to adjust for confounding factors such as age, race, interpregnancy interval and previous adverse outcome in first pregnancy.

Parity and previous diabetes mellitus were adjusted for in this review, which included only primiparous women (from parity 0 to 1) with no previous history of type II diabetes mellitus (T2DM) or GDM in previous pregnancy. Compared with low multiparity, primigravid women have different risks and complications whilst higher parity (parity 4 upwards) has been associated with increased obstetric complications and neonatal morbidity.[40] Furthermore, T2DM during pregnancy is associated with higher risks of stillbirth, perinatal mortality and congenital malformations.[42] Excluding these factors and taking into account that all papers included in this review were adjusted for multiple confounding variables means that there is a reduced possibility that the results are due to chance. Further, this review aimed to minimise heterogeneity in several ways: each study was assessed according to if confounding factors were appropriately recognised and adjusted for, weight change was stratified into three categories in order to effectively combine results that could be compared, and sensitivity analysis was carried out by removing low quality studies with a high level of bias.

Limitations

Despite attempts to limit heterogeneity as described above, the high heterogeneity means that it may be misleading to combine results to provide an average estimate of exposure. Conclusions should therefore be interpreted with caution and considered largely hypothesis-generating. A random-effects model was used rather than a fixed effect model to assess heterogeneity in the meta-analysis as it considers in-between study variation. Further statistical analysis to assess heterogeneity such as meta-regression was not performed due to the limited number of studies for each outcome, however possible sources of heterogeneity are listed in table 4. Many of the studies report missing data and have categorised BMI change differently (for example units, groups or percentages), making it difficult to combine data in a meaningful way. However, this was addressed with subgroup analysis and by stratifying weight change into categories. The use of observational cohort studies means that it is very difficult to adjust for all possible confounding factors, leading to an inevitable heterogeneity between studies.

Table 4: Possible reasons to explain high heterogeneity (I^2) found in the review

Possible sources of heterogeneity	Example
Classification of BMI change	Units (kg/m^2), groups (underweight, obese)
Different population design	Sources of data varied, locations of studies varied
Differences in study design	Use of self-report for height and weight
Missing data	Missing data in original studies could not be controlled for
Small number of studies for each outcome	Between 2 to 4 studies for each outcome
Unknown factors (residual confounding variables)	Breastfeeding, genetic factors, diet, exercise

BMI is closely linked to lifestyle factors, diseases, and genetic traits that are correlated with the outcome of pregnancy. Although studies adjusted for multiple confounding factors, there are additional confounders that could affect results that were not adjusted for, including breastfeeding, diet, exercise and genetics. In addition, the effect of obesity may be confounded by several comorbidities that are possibly undiagnosed. Breastfeeding is a confounding factor in interpregnancy weight change as women who breastfeed have less weight post-partum, which is thought to be due to the high calorie usage during breastfeeding.[41] The lack of information regarding diet and exercise means that the reduced risk of adverse outcomes in pregnancy may not be due to the weight loss but to other aspects that are changed in a healthier lifestyle. Furthermore, interpregnancy interval and gestational weight gain were adjusted for in some studies but the effect of these should not be underestimated. The shorter the interpregnancy interval, the higher the risk of LGA.[42] The shorter the time between pregnancies or the more gestational weight gain, the more difficult it may be for women to lose the weight gained from the previous pregnancy. All future studies should adjust for interpregnancy interval and gestational weight gain.

This review focused on singleton births from parity 0 to 1, with all of the studies coming from high-income Western countries. This limits the generalisability of the conclusions to lower income countries. Even though this review did exclude women with previous GDM or type 2 diabetes mellitus, it should be noted that due to the lack of a universal screening for GDM, some women with GDM may have been missed. This is difficult to assess and control, and due to the controversy surrounding screening for GDM and the lack of good quality evidence-based data, it has been unable to be determined whether or not screening would have an important effect on adverse pregnancy outcomes.[43]

Future Research

This review highlights that observational studies can help give direction for future research. To help clarify the association between interpregnancy weight change and adverse pregnancy outcomes, a precise way of measuring BMI change needs to be implemented. Due to the problems with low rate of outcome, large studies free of bias associated with recall and self-report need to be undertaken.

Large-scale studies on specific classes of obesity should be conducted to study the rate of weight change and if it affects the magnitude of association. The National Institute for Health Research submitted a call for research regarding weight management after pregnancy, stating that excessive gestational weight gain or postpartum weight retention may be cumulative over successive pregnancies.[44] The SWAN feasibility study (Supporting Women with Postnatal Management) is aiming to study women allocated to an intervention (weight management group) or control group at 36 weeks of pregnancy and followed up 12 months postnatally. This will be one of the first studies to look at postnatal intervention in weight control in the UK.[45] Furthermore, Slimming World undertook a study in Cardiff called HELP (Health Eating and Lifestyle in Pregnancy) to look at the benefits of behaviour changes and weight management during pregnancy in the UK. The study was underpowered but healthy eating and lifestyle intervention was acceptable to help women control their weight change during pregnancy and postpartum.[46] Other feasibility studies such as PRAM (Pregnancy and Weight Monitoring) are currently underway and evaluation of the efficacy of these interventions is expected in the future.[47]

Implications for policy makers and clinicians

NICE postnatal guidelines currently suggest that women with a BMI > 30 kg/m^2 at the 6-8 week postnatal check are referred for advice regarding weight loss. This review provides some evidence to suggest that postnatal weight interventions are needed, as even moderate changes in interpregnancy BMI can lead to increased risks of adverse pregnancy outcomes for the mother and baby.

The Institute of Medicine has introduced optimal weight gain for BMI-specific ranges in pregnancy, though NICE has recommended that these guidelines should be researched to see if they are appropriate for the UK population.[48] Based on the results of this review, it can be suggested that clinicians should be aware of the risk in women whose BMI has changed after their first pregnancy. Particularly women who wish to conceive again shortly after birth of their first child should be monitored after pregnancy to attempt to keep BMI change to a minimum. Additionally, a decrease in weight for obese and overweight women is beneficial and lowers the risk of GDM, LGA and c-section. Therefore, not only is monitoring gestational weight change important in preventing adverse outcomes in pregnancy, but interpregnancy weight change can also influence maternal and foetal outcomes.

CONCLUSION

This study is the first systematic review and meta-analysis to assess the effect of interpregnancy weight change on six adverse pregnancy outcomes. The results show that interpregnancy weight gain increases the risk of GDM, CS and LGA, while weight reduction lowers the risk of GDM and LGA. In particular, it is noted that weight gain from normal weight is more detrimental than from a higher weight in regards to GDM, LGA and c-section. Clinicians should aim to address weight change after birth of the first child in order to lower risk of adverse pregnancy outcomes. Highest risks were noted in obese and overweight patients, thus weight reduction in between pregnancies is important for risk prevention of adverse outcomes such as GDM, macrosomia and LGA. However, further research is needed to substantiate the evidence presented in this review.

FOOTNOTES

Contributors: EO formulated the research question and wrote and reviewed the report. SM did the literature search, extracted and selected articles, did the meta-analysis, and wrote the report. OS did the literature search, extracted and selected articles, and contributed to writing the paper. PS did the meta-analysis. DB and LP contributed to the writing of the paper.

Funding: EO is partly funded by the Big Lottery Fund, NIHR, Tommy's Charity and Guy's and St Thomas' Charity. LP is partly funded by Tommy's Charity. PS is partly funded by CLAHRC South London (NIHR) and Tommy's Charity.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: None required

Data sharing: No additional data available

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

REFERENCES

1. Yu Z, Han S, Zhu J, Sun X, Ji C. Pre-Pregnancy Body Mass Index in Relation to Infant Birth Weight and Offspring Overweight/Obesity: A Systematic Review and Meta-Analysis. PLoS ONE 2013; 8: e61627.
2. Chu SY, Kim SY, Lau J, Schmid CH, Dietz PM, Callaghan WM, Curtis KM. Maternal obesity and risk of stillbirth: a metaanalysis. Am J Obstet Gynecol. 2007; 197: 223–8.
3. Jovanovič L, Liang Y, Weng W, Hamilton M, Chen L, Wintfeld N. Trends in the incidence of diabetes, its clinical sequelae, and associated costs in pregnancy. Diabetes/Metabolism Research and Reviews. 2015; 31: 707–716.
4. Balen AH, Anderson RA, Policy & Practice Committee of the BFS. Impact of Obesity on female reproductive health: British Fertility Society, Policy and Practice Guidelines. Hum Fertil (Camb). 2007; 10: 195–206.
5. Leddy MA, Power ML, Schulkin J. The Impact of Maternal Obesity on Maternal and Fetal Health. Reviews in Obstetrics and Gynecology. 2008; 1: 170–178.
6. Oteng-Ntim E, Varma R, Croker H, Poston L, Doyle P. Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis. BMC Medicine 2012; 10: 47.
7. Centers for Disease Control and Prevention. Recommendations to improve preconception health and health care - United States: a report of the CDC/ ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. MMWR 2006; 55: 1–22.
8. Whitworth M, Dowswell T. Routine pre-pregnancy health promotion for improving pregnancy outcomes. Cochrane Database of Systematic Reviews 2009; 4: CD007536.
9. Tieu J, Bain E, Middleton P, Crowther CA. Interconception care for women with a history of gestational diabetes for improving maternal and infant outcomes. Cochrane Database of Systematic Reviews 2013; 6: CD010211.
10. PROSPERO, International prospective register of systematic reviews. [Internet]. York: Centre for Reviews and Dissemination [cited 22 June 2016]. Available from: http://www.crd.york.ac.uk/PROSPERO
11. Cnattingius S, Villamor E. Weight change between successive pregnancies and risks of stillbirth and infant mortality: a nationwide cohort study. Lancet 2016; 387: 558–65.
12. Najafian M, Cheraghi M. Occurrence of Fetal Macrosomia Rate and Its Maternal and Neonatal Complications: A 5-Year Cohort Study. Obstet Gynecol 2012:e353791.
13. Centre for Maternal and Child Enquiries (CMACE) Maternal obesity in the UK: findings from a national project. (2010) London: CMACE.
14. American Diabetes Association. Gestational Diabetes Mellitus. Diabetes Care. 2004;27:88-90.
15. World Health Organisation body mass index (BMI) classification. (Website) Available on: www.who.int/bmi/index.jsp?introPage=intro_3.html. Last accessed 04 Feb 2017.
16. Ehrlich SF, Hedderson MM, Feng J, Davenport ER, Gunderson EP, Ferarra A. Changes in prepregnancy body mass indexes between pregnancies and the risk of gestational diabetes in a second pregnancy. Obstet Gynaecol. 2011;117: 1323–1330.
17. Getahun D, Ananth CV, Peltier MR, Salihu HM, Scorza WE. Changes in prepregnancy body mass index between the first and second pregnancies and risk of large-for-gestational-age birth. Am J Obstet Gynecol 2007;196:e1–e18.
18. Getahun D, Ananth CV, Oyelese Y, Chavez MR, Kirby RS, Smulian JC. Primary preeclampsia in the second pregnancy: effects of changes in prepregnancy body mass index between pregnancies. Obstet Gynecol 2007;110:1319–1325.
19. Jain AP, Gavard JA, Rice JJ, Catanzaro RB, Artal R, Hopkins SA. The impact of interpregnancy weight change on birthweight in obese women. Am J Obstet Gynecol. 2013;208:e1–e7.
20. Whiteman VE, McIntosh C, Rao K, Mbah AK, Salihu HM. Interpregnancy BMI change and risk of primary caesarean delivery. J Obstet Gynaecol 2011;31:589–593.

21. Whiteman VE, Aliyu MH, August EM, McIntosh C, Duan J, Alio AP, Salihu HM. Change in body mass index between pregnancies and risk of gestational and type two diabetes. Arch Obstet Gynaecol 2011;284:235–240.

22. Wallace JM, Bhattacharya S, Campbell DM, Horgan GW. Inter-pregnancy weight change impacts placental weight and is associated with the risk of adverse pregnancy outcomes in the second pregnancy. BMC Pregnancy Childbirth 2014;14: 40.

23. Wallace JM, Bhattacharya S, Campbell DM, Horgan GW. Inter-pregnancy Weight Change and risk of recurrent pregnancy complications. PLoS One 2016;11:e0154812.

24. Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. Lancet 2006;368:1164–1170.

25. Bogaerts A, Van den Bergh BR, Ameye L, Witters I, Martens E, Timmerman D, Devlieger R. Interpregnancy weight change and risk for adverse perinatal outcome. Obstet Gynaecol 2013;122:999–1009.

26. Wells G, Shea B, O'Connell J & Roberson J. 2011 The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. (Website) Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Last accessed: 28 Feb 2017

27. Higgins JPT, Altman DG, Gotzshe PC, Juni P, Moher D, Oxman AD. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;3443:d5928.

28. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.

29. Higgins JPT. Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. Int J Epidemiol 2008;37:1158-1160.

30. Higgins JPT, Altman DG, Sterne JAC (2011). Chapter 9: Meta-regression In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 ed. Higgins JPT & Green S. [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org. Last accessed: 14 Mar 2017.

31. Borenstein ML, Hedges V, Higgins JPT, Rothstein HR. (2009) Chapter 20: Meta-regression. In: Introduction to meta-analysis. Chichester: John Wiley & Sons Ltd.

32. Catalano PM. Obesity, Insulin Resistance and Pregnancy Outcome. Reproduction 2010;140:365–371.

33. Pedersen J (1952) Diabetes and pregnancy: blood sugar of newborn infants [PhD thesis], Danish Science Press, Copenhagen (Denmark)

34. Scholl TO, Sowers M, Chen X, Lenders C. Maternal Glucose Concentration Influences Fetal Growth, Gestation, and Pregnancy Complications. Am J Epidemiol 2001;154:514-520.

35. Catalano PM, Hanguel-De Mouzon S. Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic? AJOG 2011;204:479-487.

36. Di Cianni G, Miccoli R, Volpe L. Maternal triglyceride levels and newborn weight in pregnant women with normal glucose tolerance. Diabet Med 2005;22: 21–25.

37. Greene GW, Smiciklas-Wright H, Scholl TO, Karp RJ. Postpartum Weight Change: How Much of Weight Gained in Pregnancy Will Be Lost At Delivery? Obstet Gynecol 1988;71:701-707.

38. McKeown T, Record RG. The influence of weight and height on weight changes associated with pregnancy in Women. J Endocrinol 1957;15:423-429

39. Ock M, Lee S, Jo MW, Lee JY, Kim SH. Assessing Reliability of Medical Record Reviews for the Detection of Hospital Adverse Events. J Prev Med Public Health 2015;48:239–248.

40. Bai J, Wong FWS, Bauman A, Mohsin M. Parity and pregnancy outcomes. AJOG 2002;186:274-278.

41. Allen J, Hector D. Benefits of breastfeeding. N S W Public Health Bull 2005;16:42-46.

42. Zhu BP. Effect of interpregnancy interval on birth outcomes: findings from three recent US studies. Int J Gynaecol Obstet 2005;89:S25-S33.

43. Brody SC, Harris R, Lohr K. Screening for gestational diabetes: a summary of the evidence for the U.S. Preventive Services Task Force. Obstet Gynecol 2003;101:380-392.

44. National Institute of Health Research (2014) 14/67 Weight management after pregnancy. Available on: njl-admin.nihr.ac.uk/document/download/2007433 Last accessed: 14 Mar 2017

45. IRAS. Supporting Women with Postnatal Weight MAnagemeNt – SWAN Feasibility Trial Protocol. (2016) Available on: njl-admin.nihr.ac.uk/document/download/2007612 Last accessed: 14 Mar 2017

46. Jewell K, Avery A, Barber J, Simpson S. The healthy eating and lifestyle in pregnancy (HELP) feasibility study. BMJ 2014;22:727-736.

47. Sanders J (2016) PRAM. Available on: cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/pram Last accessed: 14 Mar 2017.

48. National Institute for Health and Care Exellence (2010) Weight management before, during and after pregnancy: Public health guideline. Available on: nice.org.uk/guidance/ph27 Last accessed: 14 Mar 2017

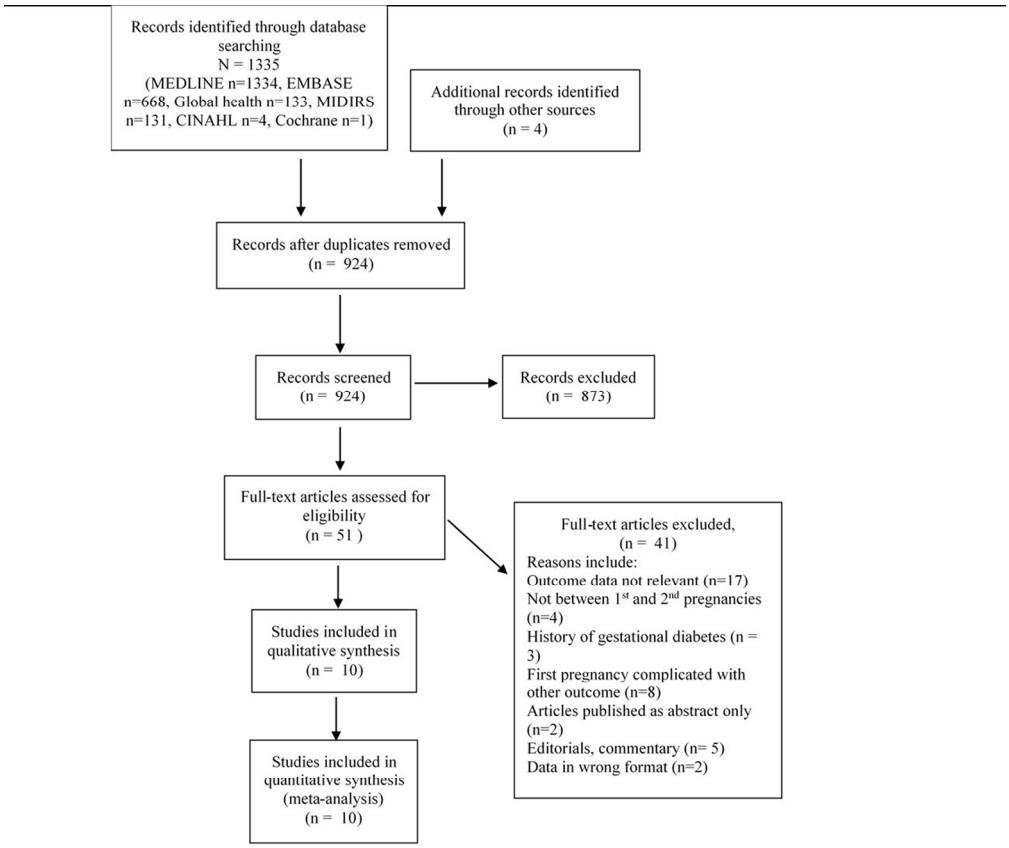

Figure 1: 2009 PRISMA flow diagram showing results of literature search

108x94mm (300 x 300 DPI)

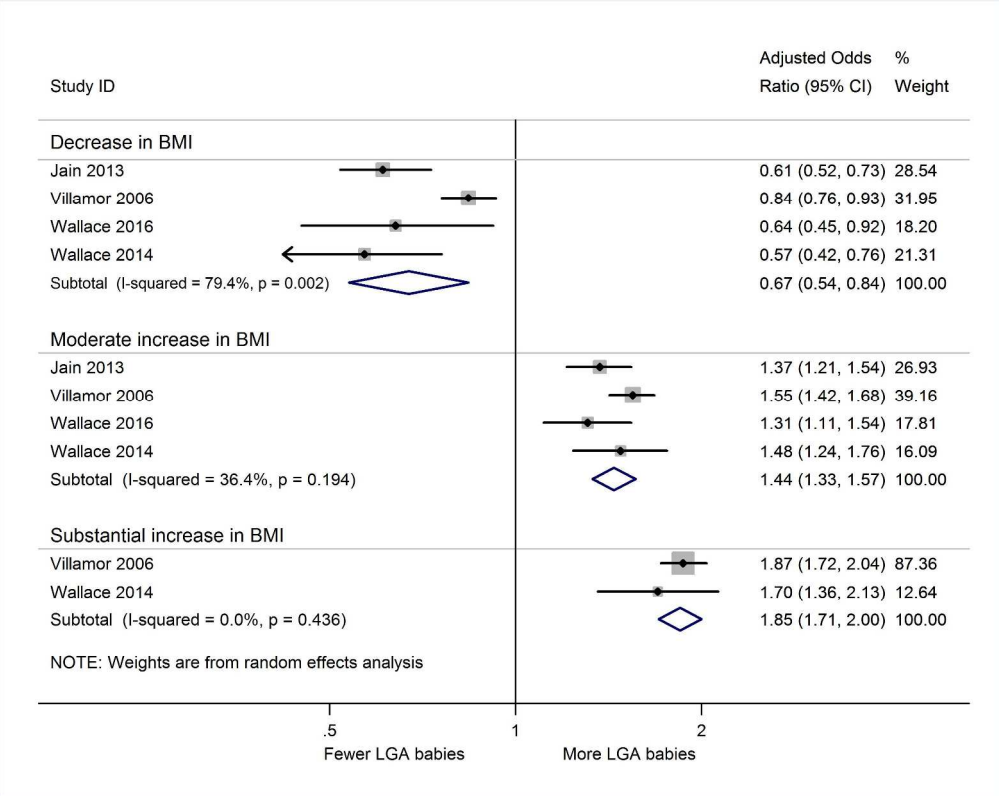

Figure 2: Forest plot showing change in interpregnancy weight compared with reference category and the risk of large for gestational age births in the subsequent pregnancy, irrespective of BMI at the beginning of the first pregnancy. (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

278x221mm (300 x 300 DPI)

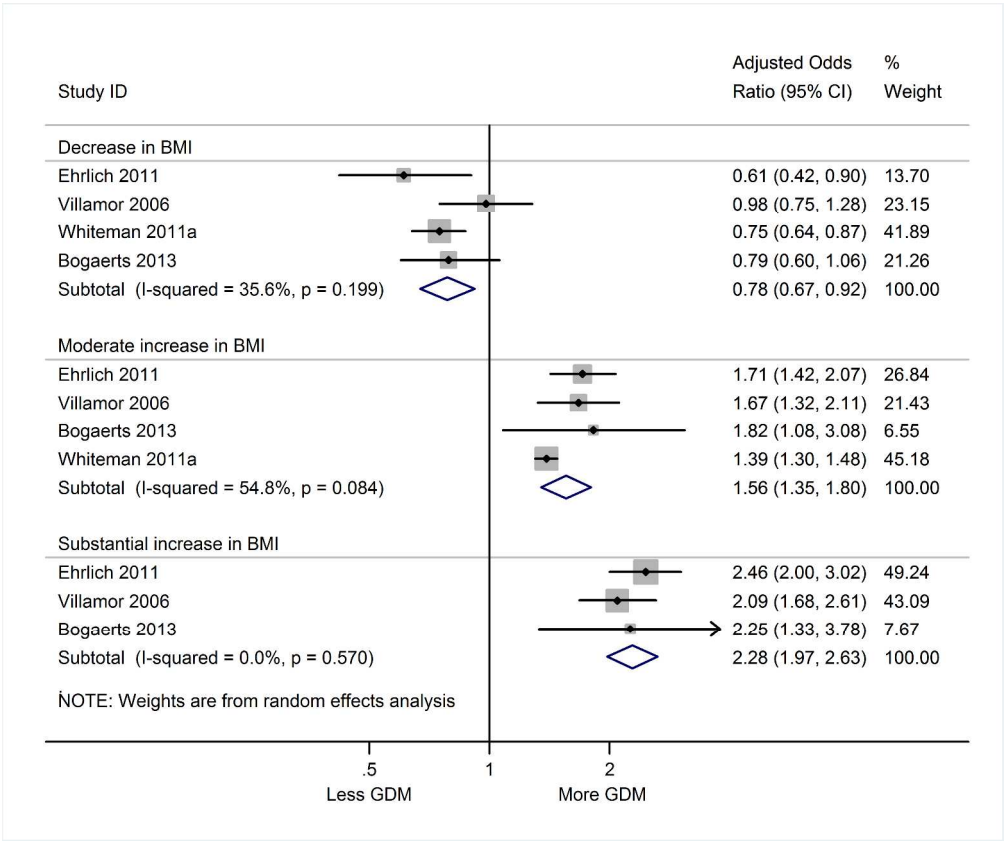

Figure 3: Forest plot showing change in interpregnancy weight compared with reference category and the risk of gestational diabetes mellitus in the subsequent pregnancy, irrespective of BMI at the beginning of the first pregnancy. (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

350x293mm (300 x 300 DPI)

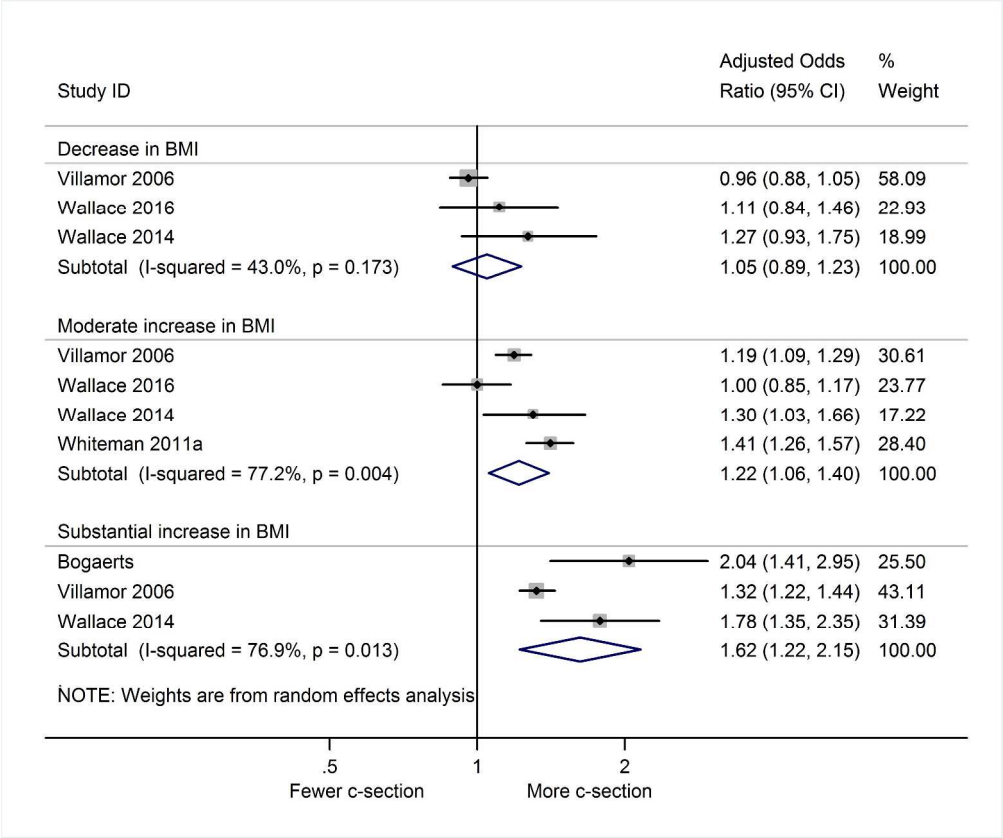

Figure 4: Forest plot showing change in interpregnancy weight with reference category and the risk of csection
in the subsequent pregnancy irrespective of BMI at the beginning of the first pregnancy. (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

APPENDIX 1

Table 5: **Criteria for the Newcastle-Ottawa Scale regarding star allocation to assess quality of studies (out of a total of seven stars)**

Criteria	Acceptable (star awarded):	Unacceptable (star not awarded):
Representativeness of exposed cohort	Population-based	Hospital-based
Selection of non-exposed cohort	Same setting as exposed cohort	Different setting from exposed cohort
Ascertainment of exposure	Secure records or directly measured	Self-reported information
Comparability	Excluded or adjusted for prior outcome in analysis	No exclusion of prior outcome in previous pregnancy
	Adjusted for age, race, smoking and interpregnancy interval	Did not adjust for age, race, smoking and interpregnancy interval
Outcome of interest	Secure records or directly measured	Self-reported information
Adequacy of follow-up	Adjusted for missing data	No statement regarding missing data

Table 6: Quality assessment of studies using a modified Newcastle-Ottawa scale for assessing studies in the systematic review of interpregnancy weight change and pregnancy outcome

Study ID	Selection			Comparability*	Outcome		Total (7⋆)
	Representativeness of exposed cohort (⋆)	Selection of non-exposed cohort (⋆)	Ascertainment of exposure (⋆)	(⋆⋆)	Assessment of outcome (⋆)	Adequacy of follow up (⋆)	
Bogaerts 2013	⋆	⋆	-	⋆⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Ehrlich 2011	-	⋆	⋆	⋆⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Getahun 2007a	⋆	⋆	-	⋆ -	⋆	-	⋆⋆⋆⋆ (4)
Getahun 2007b	⋆	⋆	-	⋆⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Jain 2013	⋆	⋆	-	⋆⋆	⋆	⋆	⋆⋆⋆⋆⋆⋆ (6)
Villamor 2006	⋆	⋆	⋆	⋆⋆	⋆	-	⋆⋆⋆⋆⋆⋆ (6)
Wallace 2014	-	⋆	⋆	⋆⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Wallace 2016	⋆	⋆	⋆	- ⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Whiteman 2011a	⋆	⋆	-	⋆⋆	⋆	⋆	⋆⋆⋆⋆⋆⋆ (6)
Whiteman 2011b	⋆	⋆	-	⋆⋆	⋆	⋆	⋆⋆⋆⋆⋆⋆ (6)

* Comparability assessed as the following: one star rewarded if study excluded or adjusted for outcome in first pregnancy, another star rewarded if study adjusted for age, race, smoking and interpregnancy interval

Table 7: Risk of bias assessment (modified from Cochrane Tool to Assess Risk of Bias in Cohort Studies and EPOC Data Collection Form)[29]

Study ID	Allocation concealment (selection bias)	Assessment of exposure (self-report)	Outcome of interest present at beginning	Incomplete data	Selective reporting (reporting bias)	Total score*
Bogaerts 2013	+	-	+	+	-	3
Ehrlich 2011	-	+	+	?	+	3
Getahun 2007a	+	-	?	?	+	2
Getahun 2007b	+	-	+	?	+	3
Jain 2013	+	-	+	+	+	4
Villamor 2006	+	+	+	?	+	4
Wallace 2014	-	+	+	?	+	3
Wallace 2016	+	+	-	?	+	3
Whiteman 2011a	+	-	+	+	+	4
Whiteman 2011b	+	-	+	+	+	4

*Total score: points awarded based on number of "+" or low risk of bias
+ = Low risk of bias, ? = Unclear risk of bias, - = High risk of bias

APPENDIX 2

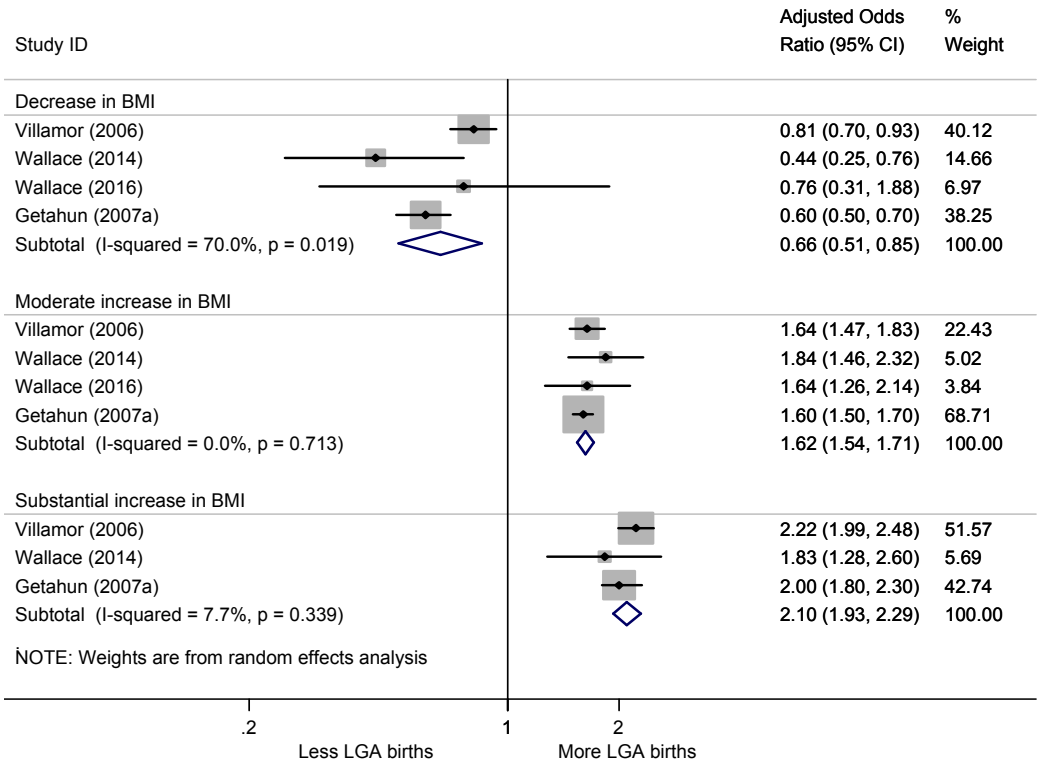

Figure 5: Forest plot showing change in interpregnancy weight compared with reference category and the risk of large for gestational age births in the subsequent pregnancy for women with normal BMI (< 25) at the beginning of first pregnancy (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

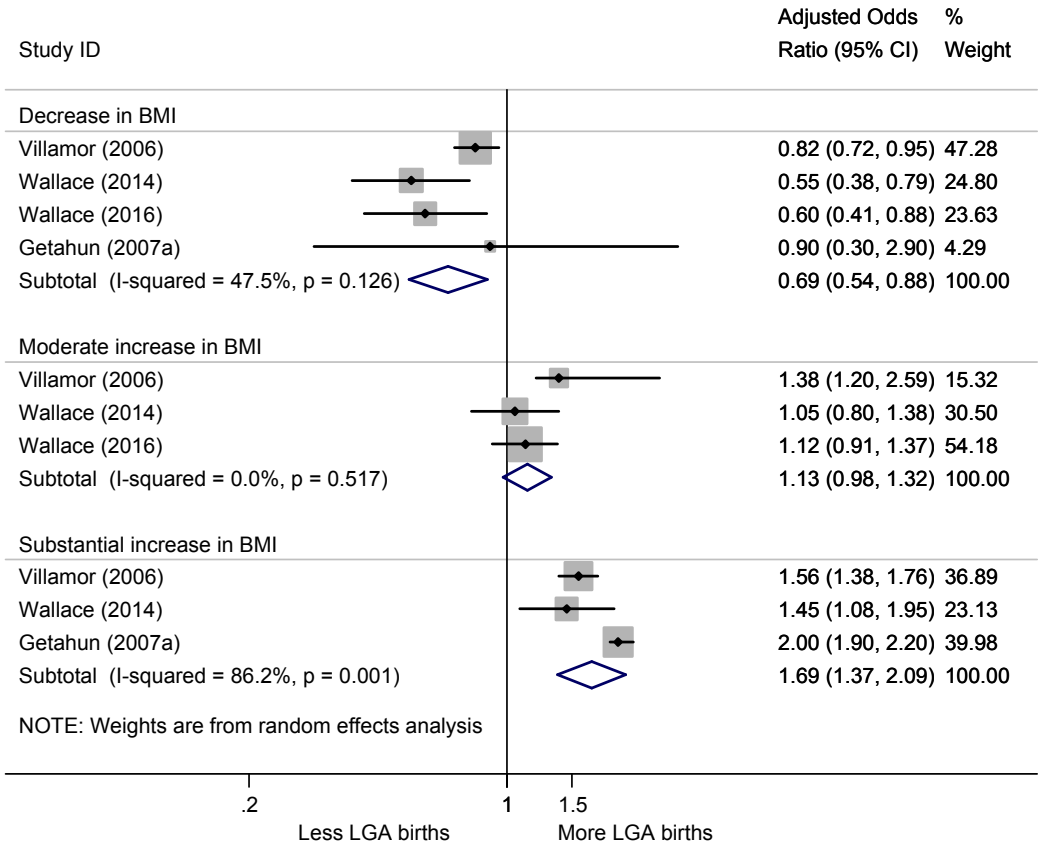

Figure 6: Forest plot showing change in interpregnancy weight compared with reference category and the risk of large for gestational age births in the subsequent pregnancy for women with overweight/obese BMI (≥ 25) at the beginning of first pregnancy (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

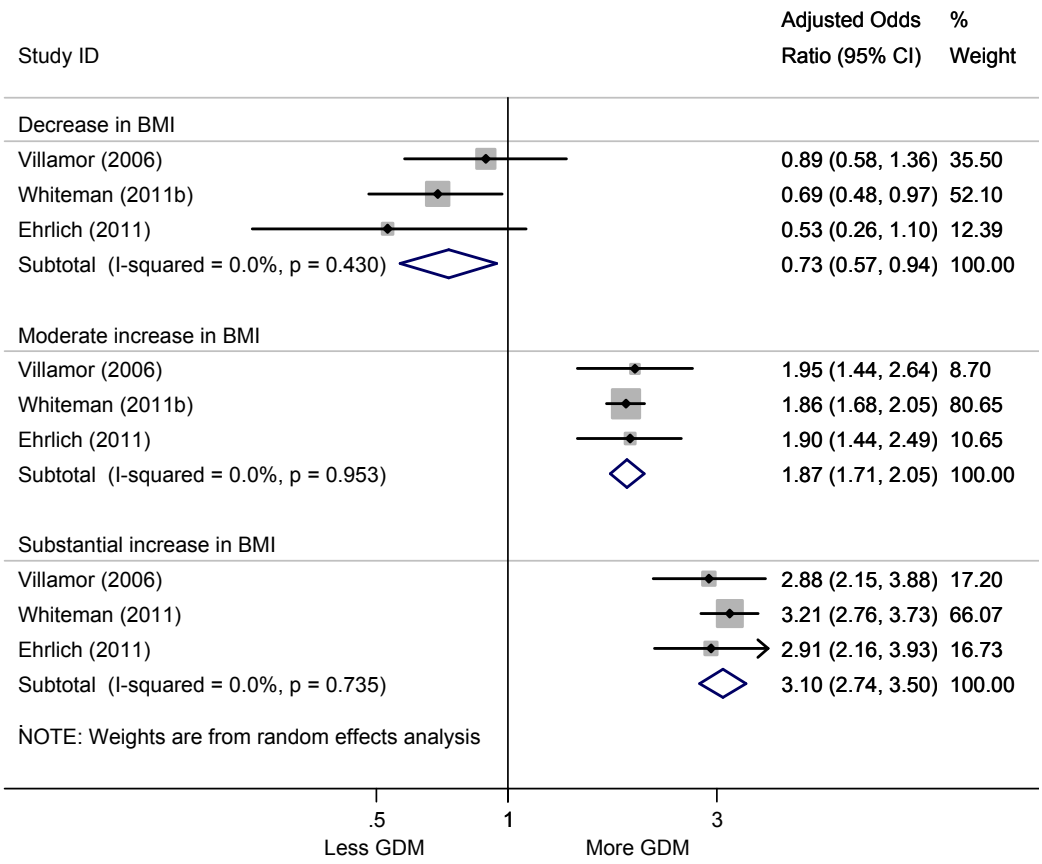

Figure 7: Forest plot showing change in interpregnancy weight compared with reference category and the risk of gestational diabetes mellitus in the subsequent pregnancy for women with normal BMI (< 25) at the beginning of first pregnancy (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

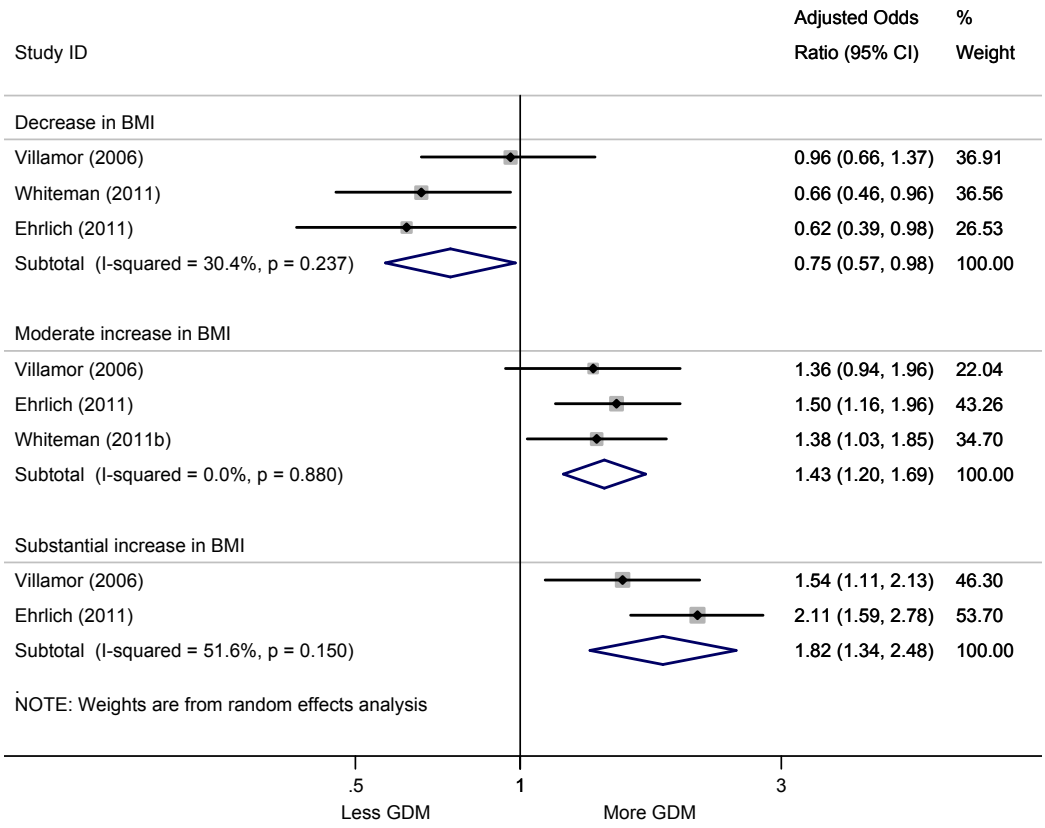

Figure 8: Forest plot showing change in interpregnancy weight compared with reference category and the risk of gestational diabetes mellitus in the subsequent pregnancy for women with overweight/obese BMI (≥ 25) at the beginning of first pregnancy (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

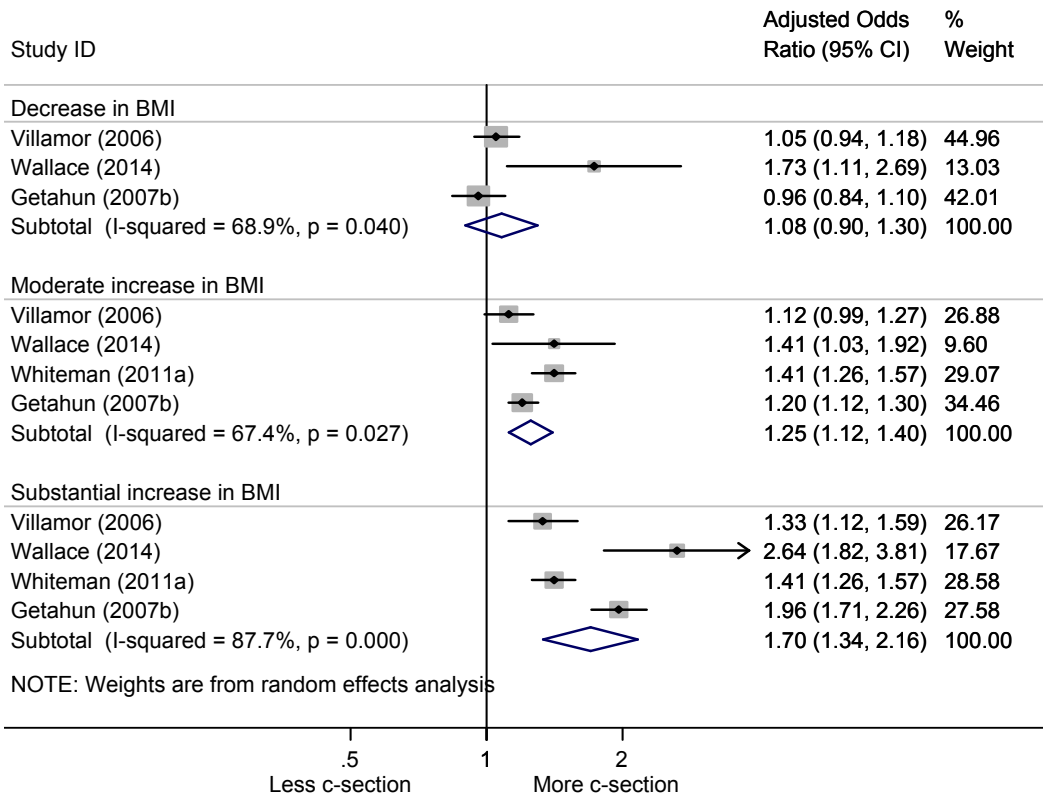

Figure 9: Forest plot showing change in interpregnancy weight compared with reference category and the risk of C-section in the subsequent pregnancy for women with normal BMI (< 25) at the beginning of first pregnancy (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

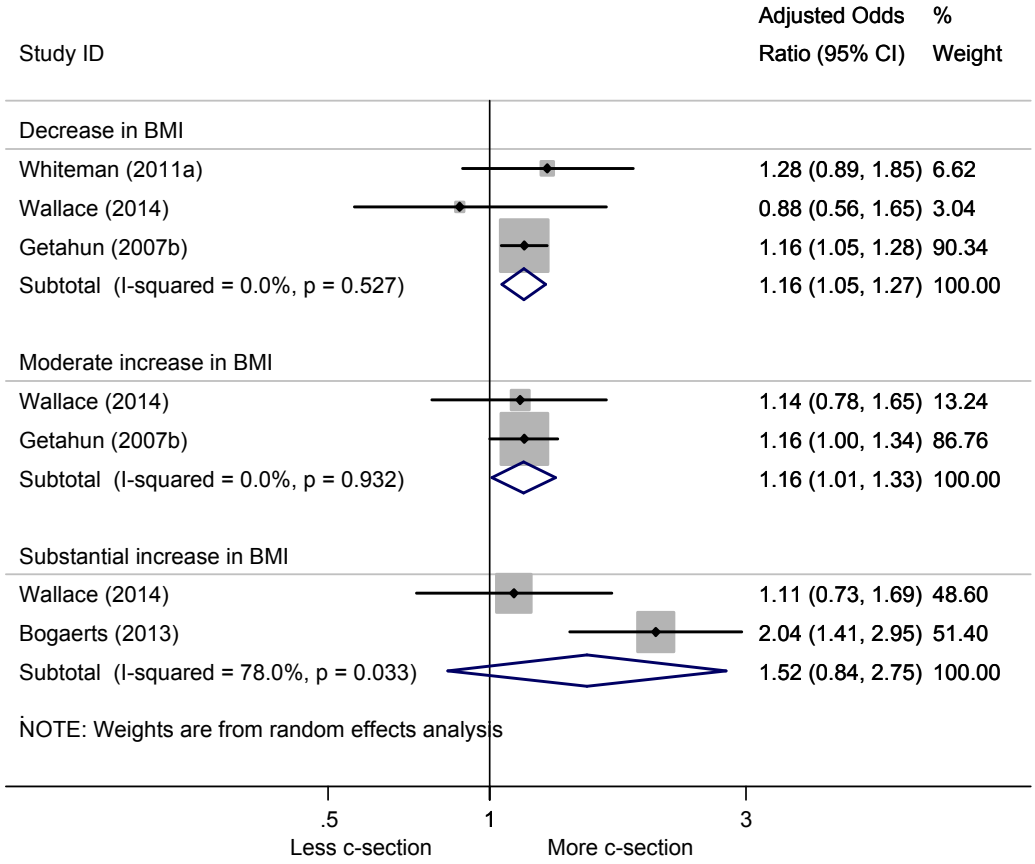

Figure 10: Forest plot showing change in interpregnancy weight compared with reference category and the risk of C-section in the subsequent pregnancy for women with overweight/obese BMI (≥ 25) at the beginning of first pregnancy (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

APPENDIX 3

Table 8: Overall statistical significance of effect size = 1

Outcome	Change in BMI	Z value	P-value
LGA	Decrease	z= 7.02	p = 0.000
	Moderate increase	z= 12.47	p = 0.000
	Substantial increase	z= 15.09	p = 0.000
Macrosomia	Decrease	z= 2.46	p = 0.014
	Moderate increase	z= 3.76	p = 0.000
	Substantial increase	z= 1.72	p = 0.086
GDM	Decrease	z= 3.03	p = 0.002
	Moderate increase	z= 6.02	p = 0.000
	Substantial increase	z= 11.16	p = 0.000
C-section	Decrease	z= 0.55	p = 0.579
	Moderate increase	z= 2.74	p = 0.006
	Substantial increase	z= 3.33	p = 0.001

Table 9: Overall statistical significant of effect size = 1 in subgroups of women with a BMI before pregnancy of < 25 or ≥ 25

Outcome	Change in BMI	Z value	P-value
LGA BMI < 25	Decrease	z= 3.18	p = 0.001
	Moderate increase	z= 18.27	p = 0.000
	Substantial increase	z= 17.7	p = 0.000
LGA BMI ≥ 25	Decrease	z= 2.94	p = 0.003
	Moderate increase	z= 1.64	p = 0.102
	Substantial increase	z= 4.87	p = 0.000
GDM BMI < 25	Decrease	z= 2.11	p = 0.035
	Moderate increase	z= 4.03	p = 0.000
	Substantial increase	z= 3.83	p = 0.000
GDM BMI ≥ 25	Decrease	z= 2.42	p = 0.016
	Moderate increase	z= 13.75	p = 0.000
	Substantial increase	z= 18.11	p = 0.000
C-section BMI < 25	Decrease	z= 0.82	p = 0.415
	Moderate increase	z= 4.02	p = 0.000
	Substantial increase	z= 4.33	p = 0.000
C-section BMI ≥ 25	Decrease	z= 3.05	p = 0.002
	Moderate increase	z= 2.10	p = 0.036
	Substantial increase	z= 1.37	p = 0.170

APPENDIX 4

Table 1: Results after sensitivity analysis for the effect of interpregnancy BMI change on large for gestational age births, in women with a prepregnancy BMI of < 25 and ≥ 25. (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

Prepregnancy BMI	BMI change	Number of studies	aOR (05% CI)	I^2	p-value
< 25	Decrease	3	0.674 (0.447-1.016)	54.00%	0.114
	Moderate increase	3	1.671 (1.523-1.833)	0.00%	0.672
	Substantial increase	2	2.176 (1.938-2.443)	4.00%	0.307
≥ 25	Decrease	3	0.676 (0.511-0.895)	64.50%	0.06
	Moderate increase	3	1.134 (0.975-1.319)	0.00%	0.517
	Substantial increase	2	1.544 (1.379-1.727)	0.00%	0.654

Appendix 5 table 11: PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**2**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**3**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**3**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**4**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**4**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**4**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**4**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**4**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**4-5**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**5**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**5**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**4**
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**5**

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**5**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**5**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**6**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**8-9**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**Appendix 1**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**10-13**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**10-13**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**Appendix 1**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**13**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**13**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**14**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**16**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**16**

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**2**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**3**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**3**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**4**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**4**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**4**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**4**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**4**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**4-5**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**5**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**5**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**4**
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**5**

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**5**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**5**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**6**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**8-9**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**Appendix 1**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**10-13**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**10-13**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**Appendix 1**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**13**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**13**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**14**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**16**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**16**

BMJ Open

Interpregnancy Weight Change and Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018778.R1
Article Type:	Research
Date Submitted by the Author:	20-Dec-2017
Complete List of Authors:	Oteng-Ntim, Eugene ; London School of Hygiene and Tropical Medicine Mononen, Sofia; King's College, London, Division of Reproduction and Endocrinology, Maternal and Fetal Research Unit, 10th Floor North Wing, St Thomas Hospital, SE1 7EH Sawicki, Olga; London School of Hygiene and Tropical Medicine Seed, Paul; Kings College, London, Division of Reproduction and Endocrinology, Maternal and Fetal Research Unit, 10th Floor North Wing, St Thomas Hospital, SE1 7EH Bick, Debra; Kings College London, Florence Nightingale School of Nursing and Midwifery Poston, Lucilla; Kings College, London, Division of Reproduction and Endocrinology
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	body mass index, interpregnancy, obesity, pregnancy

Interpregnancy Weight Change and Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis

Eugene Oteng-Ntim, Sofia Mononen, Olga Sawicki, Paul Seed, Debra Bick, Lucilla Poston

London School of Hygiene and Tropical Medicine, London, UK

Eugene Oteng-Ntim PhD
Associate Professor Epidemiology and Population Health
Consultant Obstetrician,

Olga Sawicki MD, MSc
Senior Scientist in UNAIDS

Division of Women's Health, King's College London, St. Thomas' Hospital, London, UK

Sofia Mononen
MBBS BSc student

Paul Seed MSc
Senior Lecturer in Medical Statistics

Prof Debra Bick PhD
Professor of Evidence Based Midwifery

Prof Lucilla Poston PhD
Tommy's Campaign Professor of Maternal and Fetal Health, Head of Division of Women's Health

Correspondence to: Dr Eugene Oteng-Ntim, Department of Women's Health, Guy's and St Thomas' National Health Service Foundation Trust, London SE1 7EH, UK, eugene.oteng-ntim@gstt.nhs.uk

ABSTRACT

Objectives: To evaluate the effect of interpregnancy BMI change on pregnancy outcomes, including large-for-gestational-age babies (LGA), small-for-gestational-age babies (SGA), macrosomia, gestational diabetes mellitus (GDM), and caesarean section.

Design: Systematic review and meta-analysis of observational cohort studies

Data sources: Literature searches were performed across Cochrane, MEDLINE, EMBASE, CINAHL, Global Health and MIDIRS databases.

Study selection: Observational cohort studies with participants parity 0 to 1.

Main outcome measures: Adjusted odds ratios (aOR) with 95% confidence intervals were used to evaluate the association between interpregnancy BMI change on five outcomes.

Results: 925,065women with singleton births from parity 0 to 1 were included in the meta-analysis of eleven studies selected from 924 identified studies. A substantial increase in interpregnancy BMI (> 3 BMI units) was associated with an increased risk of LGA (aOR=1.85, 95% CI 1.71-2.00, p<0.001), GDM (aOR=2.28, 1.97-2.63, p<0.001), macrosomia (aOR=1.54, 95% CI 0.939-2.505) and c-section (aOR=1.62, 1.36-1.94, p<0.001) compared with the reference category, and a decreased risk of SGA (aOR=0.86 95% CI 0.75-0.99, p=0.041). An interpregnancy BMI decrease was associated with a decreased risk of LGA births (aOR=0.67 95% CI 0.54-0.84,p<0.001), and GDM (aOR=0.78 95% CI 0.67-0.92, p=0.002), and an increased risk of SGA (aOR=1.40 95% CI 1.15-1.72, p=0.001). Women with a normal BMI (<25) at first pregnancy who have a substantial increase in BMI between pregnancies had a higher risk of LGA (aOR=2.10, 1.93-2.29) and GDM (aOR=3.10, 2.74-3.50) when compared to a reference than women with a BMI≥25 at first pregnancy.

Conclusions: Gaining weight between pregnancies increases risk of developing GDM, CS and LGA, and reduces risk of SGA in the subsequent pregnancy. Losing weight between pregnancies reduces risk of GDM and LGA and increases risk of SGA. Clinicians should aim to address weight change after birth of the first child to reduce risk of adverse outcomes.

Registration: PROSPERO CRD42016041299

Strengths and limitations of the study

- We believe this to be the first meta-analysis completed on the topic of interpregnancy weight change and its effect on five adverse pregnancy outcomes.
- A large sample size of 925,065women was collected from eleven well-adjusted population-based observational studies, with two methods used to assess the quality of the studies.
- Sensitivity analysis was conducted to remove low quality research, which did not change the direction of effect for any outcome.
- Limitations included limited generalisability, as the research was conducted in high-income countries and only in women from parity 0 to 1.
- Further, high heterogeneity persisted after sensitivity analysis, and additional confounders (such as breastfeeding) could affect the results.

INTRODUCTION

The associations between high pregravid body mass index (BMI) and maternal and neonatal complications are well established;[1] complications include gestational diabetes mellitus (GDM), caesarean section (CS), preeclampsia, macrosomia, prematurity, and stillbirth.[2] These outcomes are of public health importance because they add to the disease burden of women and their infants thereby increasing health care costs.[3] Mirroring the trend of the global obesity epidemic (more than half of all women of reproductive age in the UK are overweight or obese),[4] the prevalence of all these pregnancy complications has risen, as has the focus on maternal weight management as a means to improve the health of women and their children.

Previous studies have investigated the effect and impact of increased weight on adverse outcomes at all stages of the periconceptional period.[5] Lifestyle and medical interventions during pregnancy have shown little effect on pregnancy outcomes.[6] In the meantime, interpregnancy care is aimed at optimising outcomes of women and their future babies.[7] But standards are lacking[8] and, owing to the paucity of literature, systematic reviews and meta-analysis, any effect of interpregnancy care on pregnancy outcomes remains nascent.[8-10]

Despite a plausible rationale for weight management as part of interpregnancy planning, a knowledge gap exists amongst healthcare providers and women of reproductive age of the impact of weight change between pregnancies. Interpregnancy weight change is defined as the difference in BMI between first and second pregnancy recorded at the first antenatal visit.[11] Whilst the number of relevant studies has expanded in recent years, no meta-analysis has been attempted. The aim of this meta-analysis was to address this gap by examining the association between interpregnancy weight change and the most prevalent associated adverse pregnancy outcomes: GDM, CS, LGA and SGA babies in the next pregnancy (see table 1 for definitions). Where possible, the data were divided according to maternal BMI <25 kg/m^2 and BMI ≥25 kg/m^2, in order to address effects of interpregnancy weight change in the overweight/obese population compared to women with a normal BMI. Only the first two successive pregnancies were assessed in order to minimise confounding due to any effects of parity on pregnancy outcome.

Table 1: **Definitions of maternal and foetal outcomes used throughout this review**

Outcome	*Definition*
Large for gestational age (LGA)	A baby with birth weight ≥90th percentile of all babies with same gestational age[2]
Small for gestational age (SGA)	A baby with birth weight <10th percentile of all babies with same gestational age[2]
Macrosomia	Birth weight of >4000g[12]
Caesarean section	Surgical incision into abdominal and uterine wall to achieve delivery of the baby[13] Only emergency CS was considered in this study.
Gestational diabetes mellitus (GDM)	Any degree of glucose intolerance with onset or first recognition during pregnancy[14]

METHODS

Protocol and registration

The study was registered in PROSPERO International prospective register of systematic reviews (CRD42016041299). The criteria outlined in the PRISMA statement and the MOOSE checklist was adhered to.

Information sources

Electronic databases including CINAHL, EMBASE, MEDLINE, the Cochrane Database of Systematic Reviews, MIDIRS and Global Health were searched from January 1990 to January 2017. Searches were limited to studies in humans. There were no language constraints. In addition, references from bibliographies and citations were manually searched. A grey literature search was run until January 1, 2017 across the following clinical trials registries: TRIP Database, EThOS, WHO International Clinical Trials Registry Platform Search Portal and the EU Clinical Trials Register.

Table 2: Search strategy for MEDLINE

1	exp birth intervals/
2	(interpregnan* or inter-pregnan* or (birth adj interval) or (between adj pregnan*) or (successive adj pregnan*) or interbirth or (pregnan* adj spacing) or (pregnan* adj interval) or (birth adj spacing) or interdelivery or (consecutive adj pregnan*) or (following adj pregnanc*) or (subsequent adj pregnan*)).mp.
3	1 or 2
4	((body adj weight) or body mass index or BMI or (weight adj change) or (weight adj los*) or (weight adj decrease) or (weight adj gain*) or (weight adj increase) or (BMI adj change) or (body adj mass adj index) or (body adj weight adj change)).mp.
5	((pregnancy adj complication) or (f?etal adj outcome) or (pregnancy adj outcome) or (adverse adj outcome) or macrosomia or large for gestational age or LGA or large-for-gestational-age or (birth adj weight) or SGA or small for gestational age or small-for-gestational-age or GDM or (gestational adj diabetes) or c-section or (c?esarean adj section).mp.
6	3 and 4 and 5
7	Limit 6 to humans

Search strategy

A search strategy was developed for MEDLINE (see table 2) and adapted for other databases. The following combination of MeSH terms and free text were used: interpregnancy, prepregnancy, weight gain, weight loss, neonatal outcomes, and pregnancy complications.

Outcome measures

Four of the most prevalent adverse outcomes were chosen as outcomes of interest for this review. These included LGA, SGA, macrosomia, c-section (CS) and GDM (defined in table 1). Gender-specific birth weight charts were used in the research for LGA and SGA birth weights. It should be noted that throughout this paper, BMI will be referred to in groups according to the WHO and NICE BMI classifications.[15]

Study selection

Observational studies such as cohort and case-control studies were included, with studies limited to humans. Only singleton births from parity 0 to 1 were included. Studies that were restricted to women with previous diabetes diagnoses were excluded, as were studies published as conference abstracts, reviews, pharmacological or surgical interventions for weight loss, case reports or unpublished trials. Studies with first p Citations found through database searches and other searches such as browsing bibliographies were combined and duplicates excluded.

Data collection and extraction

The Cochrane Good Practice Data Extraction Form was used for extracting relevant data of each study. Raw data was collected where available or calculated from the information given. Adjusted odds ratios and confidence intervals were extracted from all papers. Additional information collected from studies included: first author's name and year of publication, study design, setting, study period, sample size, outcomes, inclusion/exclusion criteria, quality assessment and population demographics and factors that each study adjusted for (including age, race, socioeconomic status, interpregnancy interval, previous maternal disease, gestational weight gain and education level).

To study whether association between change in body weight and adverse outcomes differed, study groups were classified as "substantial increase in BMI", "moderate increase in BMI" and "decrease in BMI". These groups were defined as BMI increase of more than 3 units (substantial increase), BMI increase between 1 and 3 units (moderate increase) and BMI decrease more than 1 units (decrease). If an outcome had small number of studies, substantial increase and moderate increase were combined as "increase in BMI". Studies that reported results based on WHO classification were converted into substantial, moderate and decrease in BMI where possible.

Interpregnancy weight change was defined as the prepregnancy BMI before first pregnancy to the prepregnancy BMI before second pregnancy. For each outcome, the association of BMI change on adverse pregnancy outcome was compared to the reference category, which was defined as women who maintained BMI between pregnancies or had a BMI change between -1 to 1 units.

Two investigators (SM, OS) independently performed the literature search, assessed the eligibility and quality of the retrieved papers, and performed the data extraction. The two authors compared the results and disagreements were resolved by a third reviewer (EO).

Risk of bias assessment

To assess the quality of the studies, a modified Newcastle-Ottawa scale and a Cochrane analysis of bias were performed. Sensitivity analysis was performed by removing studies with a NOS score (≤4 stars) or a high level of bias (<3 points) according to the Cochrane analysis.

Statistical analysis

Forest plots were made for each outcome to assess overall effect size and heterogeneity using Stata SE 14 (StataCorp, College Station, Texas, USA). Random effects model was used to account for variability across studies. Study weight was calculated using the inverse variance method. Data was pooled and heterogeneity assessed with the I^2 statistic, with a high heterogeneity defined as being over 50%. Results were considered statistically significant if p was less than 0.05. Sensitivity analysis was performed by removing low quality studies. Analysis was then repeated and results compared.

Role of funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Patient Involvement

No patients were involved in setting the research question or the outcome measures, and no patients were involved in developing plans for design or implementation of the study. Further, no patients were asked to advice on interpretation or writing up of results. Since this meta-analysis used aggregated data from previous trials, it is unable to disseminate the results of the research to study participants directly.

RESULTS

Literature search results

Results from the literature search came back with ten studies to be included in the qualitative synthesis. The 2009 PRISMA flow diagram can be seen in figure 1, showing the process of study selection.

Study characteristics

Study characteristics can be found in table 3. Out of the studies, one was from Belgium[16], seven were from USA[17,18,19,20,21,22,23], two from Scotland[24,25], and one from Sweden[26]. Four papers studied GDM, five papers studied LGA, four papers studied SGA, one paper studied macrosomia, and six papers studied c-section (table 3). All studies presented their data in adjusted odds ratios (aOR). S out of the eleven studies used self-reports to record prepregnancy weight and height. All studies adjusted for confounding variables such as age, race, education and marital status with most studies also adjusting for interpregnancy interval, smoking, socioeconomic status, alcohol use, country of birth and maternal illness. About half of the prospective studies were community-based, using data found from national or state databases whilst other studies used hospital data. Studies conducted by the same authors or same country were checked to make sure the sample was not the same.

Data quality

Data quality was assessed using a modified Newcastle-Ottawa scale[27] as well as a Cochrane tool of assessing bias in studies[28]. The results of this data quality assessment can be seen in appendix 1, tables 2 and 3. The exposed cohort was defined as women with a change in interpregnancy BMI, whilst the non-exposed cohort was defined as women who maintained BMI or their BMI changed between -1 and 1 units. The criteria for allocating stars (out of a total of seven stars) awarded to each study according to this NOS criteria can be found in appendix 1 table 1. Despite authors attempting to adjust for the missing data, only five studies assessed the problem of missing data and analysed if this missing data was significant. One study[16] did not report data unless it was statistically significant, giving rise to a possible high risk of reporting bias. Self-reported assessment of exposure as well as incomplete data are the two greatest sources of bias in the studies. The total score shown in appendix 1, table 3 allows for comparison of Cochrane analysis of bias and NOS. These two assessments show good agreement; good quality studies tended to have a lower risk of bias.

Table 3: Study characteristics of studies chosen for meta-analysis and review of inter-pregnancy weight change and adverse pregnancy outcomes

Study ID	Study date	Sample size	Study setting	Study type	Relevant outcomes	BMI change measured in	Confounders adjusted for	Self-reported weight/ height	Limitations
Bogaerts[16]	2013	7,897	Belgium	Population-based retrospective cohort	GDM, c-section, macrosomia	Units (-1, -1 to 1, 2, >2, >3)	Age, marital status, alcohol use, inter-pregnancy interval and gestational weight gain	Yes	No information on prior diabetes, hypertension, smoking, family history, diet, physical activity or stress, education or ethnicity, small sample. Non-significant data excluded.
Cheng[17]	2004	14,114	USA	Population-based case-control	SGA	Increase/Decrease	Pre-pregnancy BMI, age, race, smoking, marital status, education	Yes	No information on gestational weight gain, physical activity, diet
Ehrlich[18]	2011	22,351	USA	Population-based retrospective cohort	GDM	Units (>-2, -1 to -2, 0-1, 1-1.9)	Pre-pregnancy BMI, age, race, place of birth, GDM in 1st pregnancy, inter-pregnancy interval	No	No information on gestational weight gain, family history, physical activity, diet, breastfeeding
Getahun[19]	2007a	146,227	USA	Population-based retrospective cohort	LGA	Groups (underweight, normal, overweight, obese)	Age, race, education, marital status, inter-pregnancy interval, smoking, alcohol	Yes	No information on family history, diet, physical activity or stress
Getahun[20]	2007b	113,789	USA	Population-based retrospective cohort	C-section	Groups (underweight, normal, overweight, obese)	Age, race, education, marital status, inter-pregnancy interval, smoking, alcohol, previous c-section	Yes	No information on family history, diet, physical activity or stress
Jain[21]	2013	10,444	USA	Population-based retrospective cohort	LGA, SGA	Weight loss/weight gain	Pre-pregnancy BMI, age, race, ethnicity, marital status, socioeconomic status, education, inter-pregnancy interval	Yes	No information on family history, diet, physical activity or stress
Villamor[26]	2006	207,534	Sweden	Population-	GDM,	Units (<-1, -1	Age, smoking, pre-pregnancy BMI,	No	No information for family

Study ID	Study date	Sample size	Study setting	Study type	Relevant outcomes	BMI change measured in	Confounders adjusted for	Self-reported weight/ height	Limitations
				based retrospective cohort	LGA, c-section,	to 1, 1 to <2, 2 to <3, >3)	country of origin, education, inter-pregnancy interval, complications of first pregnancy		history, diet, physical activity or stress.
Wallace[24]	2014	12,740	Scotland	Population-based retrospective cohort	LGA,SGA, c-section	Units, >-2, -2 to +2 and >2	Age, smoking, inter-pregnancy interval, complications of first pregnancy	No	Low event rate, no information for family history, diet, physical activity or stress
Wallace[25]	2016	24,450	Scotland	Population-based retrospective cohort	LGA, SGA, c-section	Units, >-2, -2 to +2 and >2	Age, smoking, inter-pregnancy interval, complications of first pregnancy	No	Low event rate, no information for family history, diet, physical activity or stress, maternal weight late in pregnancy not measured
Whiteman[22]	2011a	100,828	USA	Population-based retrospective cohort	C-section	Groups (underweight, normal, overweight, obese)	Age, race, education, marital status, smoking, alcohol use, inter-pregnancy interval	Yes	Use of vital statistics data, no information for family history, diet, physical activity or stress
Whiteman[23]	2011b	232,272	USA	Population-based retrospective cohort	GDM	Groups (underweight, normal, overweight, obese)	Age, race, education, marital status, smoking, alcohol use, inter-pregnancy interval	Yes	Inability to separate GDM from type 2 diabetes, no information for family history, diet, physical activity or stress

Outcomes

A decrease in BMI (>1 BMI unit) was associated with a 33% reduction in LGA births (aOR 0.67 (95% CI 0.54-0.84), I^2=79.4%), whilst a moderate increase in BMI is associated with a 44% higher risk of LGA birth compared with the reference category (aOR 1.44 (95% CI 1.33-1.57), I^2=36.4%). A significant increase in BMI, defined as being an increase of over 3 units, had the highest risk of LGA birth (aOR=1.85 (95% CI 1.71-2.00), I^2=0%) (figure 2). Z-values and p-values for these results (appendix 2 table 1) show that all three pooled estimates were statistically significant (p<0.001).

Only one study included macrosomia as an outcome[16]. Their results showed that decrease in BMI had a reduced risk of macrosomia, aOR=0.5 (0.35-0.71), with a substantial increase in BMI associated with a higher risk of macrosomia (aOR=1.537(0.939-2.505).

A decrease in BMI (>1 BMI unit) resulted in a decreased risk of GDM (aOR 0.78 (95% CI 0.67-0.92), I^2=35.6%). A moderate increase in BMI was associated with a 56% increased risk of GDM (aOR 1.56 (95% CI 1.35-1.80), I^2=54.8%). A substantial increase in BMI (more than 3 units) was similarly associated with a high risk of GDM (aOR 2.28 (95% CI 1.97-2.63), I^2=0.0%) (figure 3). P-values for these pooled results were statistically significant for decrease (p=0.002) moderate (p<0.001) and substantial increase in BMI (p<0.001) and risk of GDM (appendix 2 table 1).

No association was observed between a decrease in BMI and risk of c-section births (aOR 1.05 (95% CI 0.89-1.23), I^2=43.0%, p=0.579, appendix 2), whilst a moderate increase and substantial increase in BMI were associated with higher risks of c-section (aOR 1.17 (95% CI 1.09-1.26) I^2=39.8%) and aOR 1.62 (1.36-1.94) I^2=85.8%), respectively) (figure 4). Both moderate and substantial increase in BMI were statistically significant (p<0.001) (appendix 2 table 1).

A decrease in BMI (>1 BMI unit) was associated with an increase in SGA births (aOR 1.40 (95% CI 1.15-1.72, I^2=64.7%), whilst an increase in BMI was associated with a decreased risk of SGA births compared with the reference category (aOR 0.86 (95% CI 0.75-0.99) (figure 5). Both of these results are statistically significant (p<0.001 and p=0.003, respectively (appendix 2 table 1).

Outcomes grouped by BMI before first pregnancy

Some studies divided women into women with a BMI of less than 25 at their first pregnancy (normal) and women with a BMI over 25 at their first pregnancy (overweight/obese).

Women of normal BMI (<25) at beginning of first pregnancy are at a higher risk of LGA babies if they have a substantial increase of BMI (OR 2.10 (95% CI 1.93-2.29), I^2=7.7%) compared with women who had an overweight/obese BMI (≥25) at the beginning of first pregnancy (OR 1.69 (95% CI 1.37-2.09), I^2=86.2%) (see appendix 2 table 2 for statistical significance). The same trend is apparent in a moderate increase of BMI (an increase of between 1 and 3 units) (refer to appendix 3 fig 1 and 2).

Women of normal BMI (<25) at beginning of first pregnancy are at a higher risk of GDM if they have a substantial increase of BMI (OR 3.10 (95% CI 2.74-3.50), I^2=0.0%) compared with women who had an overweight/obese BMI (≥ 25) at the beginning of first pregnancy (OR 1.82 (95% CI 1.34-2.48), I^2=51.6%) (appendix 3 fig 3 and 4). The same trend is apparent in a moderate increase of BMI.

Women of normal BMI (<25) at beginning of first pregnancy are at a higher risk of c-section if they have a substantial increase of BMI (OR 1.70 (95% CI 1.34-2.16), I^2=87.7%) compared with women who had an overweight/obese BMI (≥ 25) at the beginning of first pregnancy (OR 1.52 (95% CI 0.84-2.75), I^2=78.0%) (appendix 3 fig 5 and 6). The same trend is apparent in a moderate increase of BMI. However, the confidence intervals of these two odds ratios overlap and therefore the statistical significance can be questioned.

Sensitivity analysis

Sensitivity analysis was assessed by removing studies that had a high level of bias (<3 on the Cochrane analysis of bias) or were of low quality according to the Newcastle-Ottawa scale (≤4 stars). Removal of low quality studies made limited difference to the results and the direction of effect remained the same. For LGA in women with a BMI < 25 (appendix 4 table 1), results before removal of studies included decrease in BMI (aOR 0.66 (0.51-0.85), I^2=70%), moderate increase in BMI (aOR 1.62 (1.54-1.71), I^2=0%) and substantial increase (aOR 2.10 (1.93-2.29), I^2=7.7%). After sensitivity analysis, heterogeneity for each of these groups decreased.

Heterogeneity

Generally, an I^2 value of 25% is considered low, 50% moderate and 75% high.[29] This value is thought to reflect the proportion of between-study variance not explained by sampling. When pooling results from population-based observational studies and the type of research used in this paper, it is impossible to control all possible confounders which is why a certain level of heterogeneity could be expected. As Higgins (2008) comments, if the predefined eligibility criteria and data are correct, any level of heterogeneity is acceptable, given that the authors can analyse the heterogeneous studies appropriately.[30] Analysis in this paper included random-effects analysis and sensitivity analysis. Further analysis of heterogeneity in this review is warranted; however, the Cochrane handbook recommends that meta-regression should not be completed if there are fewer than ten studies in a meta-analysis.[31] Further, it has been stated that this corresponds to ten studies for each covariate in meta-regression.[32] Due to this, the sources of heterogeneity will instead be discussed in limitations.

DISCUSSION

Major findings

This study found that an interpregnancy BMI decrease is associated with a reduced risk of LGA births (aOR 0.67 (95% CI 0.54-0.84) p<0,001), reduced risk of macrosomia (aOR 0.50 (95% CI 0.35-0.71) and GDM (aOR 0.78 (95% CI 0.67-0.92) p=0.003), and an increased risk of SGA (aOR 1.40 (95% CI 1.15-1.72, p=0.001) compared with reference category of women who retained BMI. A substantial increase in interpregnancy BMI (> 3 BMI units) is associated with an increased risk of LGA (aOR 1.85 (95% CI 1.71-2.00) p<0.001), GDM (aOR 2.28 (95% CI 1.97-2.63) p<0.001), c-section (aOR 1.62 (95% CI 1.36-1.94) p<0.001) and macrosomia (aOR 1.54 (95% CI 0.94-2.50) compared with the reference category (no weight change). An increase in BMI is associated with a decreased risk of SGA (aOR 0.86 (95% CI 0.75-0.99, p=0.041) Results did not change after sensitivity analyses removing low quality and studies with high bias. We believe this is the first systematic review and meta-analysis completed on the topic of interpregnancy weight change and adverse pregnancy outcomes in women from parity 0 to 1. When results are further analysed according to prepregnancy BMI (<25 or over 25 kg/m^2), women with a normal prepregnancy BMI at first pregnancy are at higher risk of LGA (aOR 2.10 (95% CI 1.93-2.29)) and GDM (aOR 3.10 (95% CI 2.74-3.50)) compared with women with a BMI ≥25.

Interpretation of major findings

It is known that obesity is the most common risk factor for insulin insensitivity.[33] A possible biological relation between obesity and adverse perinatal outcomes is the role of glucose and insulin insensitivity in pregnancy. The Pedersen Hypothesis, first suggested in 1952, stipulates that a higher-than-normal level of glucose (the main energy substrate of the foetus) transferred via the placenta to the foetus stimulates the release of insulin and insulin-like growth factors in the foetus, causing large for gestational age infants or macrosomic births.[34] This has been supported by research showing that high postprandial glucose concentration predicts large birth weight and hypoglycaemia is associated with growth restriction.[35]

An overweight or obese pregnant woman has a 50-60% increase in insulin insensitivity compared with a normal weighted pregnant woman.[36] Associated hyperglycaemia for the infant, as well as an increase in the release of free fatty acids and triglycerides from adipose stores have been studied to be associated with increased birth weight and adiposity of the offspring.[37] The reduction in insulin sensitivity as a result of interpregnancy weight gain may lead to higher levels of GDM, LGA, macrosomia and subsequent caesarean sections. On the contrary, weight loss and its association with increased insulin sensitivity may therefore result in reduced numbers of GDM and small for gestational age births. Studies have found that not all interpregnancy weight gain is attributed to weight gain in pregnancy: 0.45 kg can be credited to the trend of weight gain over time.[38] Research has also shown that women with a BMI ≥25 before pregnancy experience greater increases in postpartum body weight, and weight change 12 months postpartum is largely influenced by the prepregnancy body weight.[39] Interpregnancy weight gain as a result of both insufficient gestational weight loss after the previous pregnancy, combined with the normal trend of weight gain over time may have an additive or synergistic effect and result in further lowering of insulin sensitivity.

Strengths

We believe this is the first systematic review and meta-analysis completed on the topic of interpregnancy weight change and adverse pregnancy outcomes in women from parity 0 to 1 with singleton births. This review synthesised the available evidence on the association of interpregnancy weight change, defined as the difference in BMI in early pregnancy between successive pregnancies, on major complications. The findings of eleven cohort studies showed that interpregnancy weight gain was strongly associated with an increased risk of namely, GDM, CS, and large birth weight babies among all women regardless of initial BMI status, and a decrease in

risk of SGA. Conversely, interpregnancy weight loss was strongly associated with a reduced risk of GDM, and large birth weight in the second-born offspring, an increase in risk of SGA, but no detectable association with the rate of CS. The criteria outlined in the PRISMA statement and the Cochrane Handbook for Systematic Reviews of Intervention was adhered to, and this can be seen in appendix 5. Furthermore, the MOOSE checklist of recommendations for reporting meta-analyses of observational studies was followed. Results did not change even after sensitivity analyses of high methodological quality studies.

Studies included in this review were cohort studies with generally large sample sizes, resulting in a large pooled sample of almost one million women. The strengths of using these studies meant that they are population-based, with a generally representative population. Outcomes were classified in the same way in each study and for most of the outcomes it is objectively defined to classify if the outcome occurred or not, reducing a possible bias of assessment of outcome. In addition to this, the reliability of medical records has shown good level of both inter-rater and intra-rater reliability.[40] This review used two different ways of analysing the quality of studies and possible sources of bias – the Newcastle-Ottawa scale and the Cochrane analysis of bias. All studies had at least four stars on the NOS, and sensitivity analysis was performed to remove low quality studies or studies with a high bias. All studies used adjusted odds ratios to adjust for confounding factors such as age, race, interpregnancy interval and previous adverse outcome in first pregnancy.

Parity and previous diabetes mellitus were adjusted for in this review, which included only primiparous women (from parity 0 to 1) with no previous history of type II diabetes mellitus (T2DM). Compared with low multiparity, primigravid women have different risks and complications whilst higher parity (parity 4 upwards) has been associated with increased obstetric complications and neonatal morbidity.[41] Furthermore, T2DM during pregnancy is associated with higher risks of stillbirth, perinatal mortality and congenital malformations.[42] Excluding these factors and taking into account that all papers included in this review were adjusted for multiple confounding variables means that it is less likely that the results are due to confounding or systematic bias and more likely to reflect genuine causality. Further, this review aimed to minimise heterogeneity in several ways: each study was assessed according to if confounding factors were appropriately recognised and adjusted for, weight change was stratified into three categories in order to effectively combine results that could be compared, and sensitivity analysis was carried out by removing low quality studies with a high level of bias.

Limitations

Originally in the PROSPERO registration other outcomes were aimed to be included (preterm birth, pre-eclampsia, perinatal death) however there was a lack of relevant data and low-quality studies linked to these outcomes and thus these outcomes were excluded from this report. Despite attempts to limit heterogeneity as described above, the high heterogeneity means that it may be misleading to combine results to provide an average estimate of exposure, especially in light of the relatively small sample sizes in each outcome. Conclusions should therefore be interpreted with caution and considered largely hypothesis-generating. The effect of confounders could not be assessed by comparing unadjusted and adjusted odds ratios, as unadjusted data was not available nor was it possible to calculate based on the available data. A random-effects model was used rather than a fixed effect model to assess heterogeneity in the meta-analysis as it considers in-between study variation. Further statistical analysis to assess heterogeneity such as meta-regression was not performed due to the limited number of studies for each outcome, however possible sources of heterogeneity are listed in table 4. Many of the studies report missing data and have categorised BMI change differently (for example units, groups or percentages), making it difficult to combine data in a meaningful way. However, this was addressed with subgroup analysis and by stratifying weight change into categories. The use of observational cohort studies means that it is very difficult to adjust for all possible confounding factors, leading to an inevitable heterogeneity between studies. Publication bias could not be assessed due to the small amount of studies in each primary outcome, with most of the outcomes having between 2-5 studies in each category. It has been suggested that less than 10 studies is not adequate in order to complete a funnel plot and would thus be underpowered.[43]

Table 4: Possible reasons to explain high heterogeneity (I^2) found in the review

Possible sources of heterogeneity	Example
Classification of BMI change	Units (kg/m^2), groups (underweight, obese)
Different population design	Sources of data varied, locations of studies varied
Differences in study design	Use of self-report for height and weight
Missing data	Missing data in original studies could not be controlled for
Small number of studies for each outcome	Between 2 to 4 studies for each outcome
Unknown factors (residual confounding variables)	Breastfeeding, family history, diet, exercise

BMI is closely linked to lifestyle factors, diseases, and genetic traits that are correlated with the outcome of pregnancy. Although studies adjusted for multiple confounding factors, there are additional confounders that could affect results that were not adjusted for, including breastfeeding, diet, exercise and genetics. In addition, the effect of obesity may be confounded by several comorbidities that are possibly undiagnosed. Breastfeeding may be a possible confounding factor in interpregnancy weight change as women who breastfeed have less weight post-partum, which is thought to be due to the high calorie usage during breastfeeding, however this is contentious.[44] The lack of information regarding diet and exercise means that the reduced risk of adverse outcomes in pregnancy may not be due to the weight loss but to other aspects that are changed in a healthier lifestyle. Furthermore, interpregnancy interval and gestational weight gain were adjusted for in some studies but the effect of these should not be underestimated. The shorter the interpregnancy interval, the higher the risk of LGA.[45] The shorter the time between pregnancies or the more gestational weight gain, the more difficult it may be for women to lose the weight gained from the previous pregnancy. All future studies should adjust for interpregnancy interval. Gestational weight gain is responsible for interpregnancy weight gain after the first pregnancy, but is a potential mediator in the second pregnancy and therefore it is questionable whether it should be adjusted for.

This review focused on singleton births from parity 0 to 1, with all of the studies coming from high-income Western countries. This limits the generalisability of the conclusions to lower income countries. Even though this review did exclude women with previous type 2 diabetes mellitus, it should be noted that due to the lack of a universal screening for GDM, some women with GDM may have been missed. This is difficult to assess and control, and due to the controversy surrounding screening for GDM and the lack of good quality evidence-based data, it has been unable to be determined whether or not screening would have an important effect on adverse pregnancy outcomes.[46]

Future Research

This review highlights that observational studies can help give direction for future research. To help clarify the association between interpregnancy weight change and adverse pregnancy outcomes, a precise way of measuring BMI change needs to be implemented and subgroup definitions should be consistent. Due to the problems with low rate of outcome, large studies free of bias associated with recall and self-report need to be undertaken that adhere to STROBE guidelines and ICHOM standards. Future researchers should also consider the possible synergistic and additive effect of normal weight gain over time combined with insufficient gestational weight loss and how it can affect pregnancy outcomes.

Large-scale studies on specific classes of obesity should be conducted to study the rate of weight change and if it affects the magnitude of association. The National Institute for Health Research submitted a call for research regarding weight management after pregnancy, stating that excessive gestational weight gain or postpartum weight retention may be cumulative over successive pregnancies.[47] The SWAN feasibility study (Supporting Women with Postnatal Management) is aiming to study women allocated to an intervention (weight management group) or control group at 36 weeks of pregnancy and followed up 12 months postnatally. This will be one of the first studies to look at postnatal intervention in weight control in the UK.[48] Furthermore, Slimming World undertook a study in Cardiff called HELP (Health Eating and Lifestyle in Pregnancy) to look at the

benefits of behaviour changes and weight management during pregnancy in the UK. The study was underpowered but healthy eating and lifestyle intervention was acceptable to help women control their weight change during pregnancy and postpartum.[49] Other feasibility studies such as PRAM (Pregnancy and Weight Monitoring) are currently underway and evaluation of the efficacy of these interventions is expected in the future.[50]

Implications for policy makers and clinicians

NICE postnatal guidelines currently suggest that women with a BMI > 30 kg/m^2 at the 6-8 week postnatal check are referred for advice regarding weight loss. This review provides some evidence to suggest that postnatal weight interventions are needed, as even moderate changes in interpregnancy BMI can lead to increased risks of adverse pregnancy outcomes for the mother and baby.

The Institute of Medicine has introduced optimal weight gain for BMI-specific ranges in pregnancy, though NICE has recommended that these guidelines should be researched to see if they are appropriate for the UK population.[51] Based on the results of this review, it can be suggested that clinicians should be aware of the risk in women whose BMI has changed after their first pregnancy. Particularly women who wish to conceive again shortly after birth of their first child should be monitored after pregnancy to attempt to keep BMI change to a minimum. Therefore, not only is monitoring gestational weight change important in preventing adverse outcomes in pregnancy, but interpregnancy weight change can also influence maternal and foetal outcomes.

CONCLUSION

This study is the first systematic review and meta-analysis to assess the association of interpregnancy weight change on five adverse pregnancy outcomes. The results show that interpregnancy weight gain increases the risk of GDM, CS and LGA, but lowers the risk of SGA, while weight reduction lowers the risk of GDM and LGA and increases the risk of SGA. In particular, it is noted that weight gain from normal weight is more detrimental than from a higher weight in regards to GDM, LGA and c-section. Keeping weight stable between consecutive conceptions is important in order to lower risk of adverse pregnancy outcomes. However, further research is needed to substantiate the evidence presented in this review.

FOOTNOTES

Acknowledgements: We would like to thank all reviewers for their helpful comments.

Contributors: EO formulated the research question and wrote and reviewed the report. SM did the literature search, extracted and selected articles, did the meta-analysis, and wrote the report. OS did the literature search, extracted and selected articles, and contributed to writing the paper. PS did the meta-analysis. DB and LP contributed to the writing of the paper.

Funding: EO is partly funded by the Big Lottery Fund, NIHR, Tommy's Charity and Guy's and St Thomas' Charity. LP is partly funded by Tommy's Charity. PS is partly funded by CLAHRC South London (NIHR) and Tommy's Charity.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: None required

Data sharing: No additional data available

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

REFERENCES

1. Yu Z, Han S, Zhu J, Sun X, Ji C. Pre-Pregnancy Body Mass Index in Relation to Infant Birth Weight and Offspring Overweight/Obesity: A Systematic Review and Meta-Analysis. PLoS ONE 2013; 8: e61627.
2. Chu SY, Kim SY, Lau J, Schmid CH, Dietz PM, Callaghan WM, Curtis KM. Maternal obesity and risk of stillbirth: a metaanalysis. Am J Obstet Gynecol. 2007; 197: 223–8.
3. Jovanovič L, Liang Y, Weng W, Hamilton M, Chen L, Wintfeld N. Trends in the incidence of diabetes, its clinical sequelae, and associated costs in pregnancy. Diabetes/Metabolism Research and Reviews. 2015; 31: 707–716.
4. Balen AH, Anderson RA, Policy & Practice Committee of the BFS. Impact of Obesity on female reproductive health: British Fertility Society, Policy and Practice Guidelines. Hum Fertil (Camb). 2007; 10: 195–206.
5. Leddy MA, Power ML, Schulkin J. The Impact of Maternal Obesity on Maternal and Fetal Health. Reviews in Obstetrics and Gynecology. 2008; 1: 170–178.
6. Oteng-Ntim E, Varma R, Croker H, Poston L, Doyle P. Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis. BMC Medicine 2012; 10: 47.
7. Centers for Disease Control and Prevention. Recommendations to improve preconception health and health care - United States: a report of the CDC/ ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. MMWR 2006; 55: 1–22.
8. Whitworth M, Dowswell T. Routine pre-pregnancy health promotion for improving pregnancy outcomes. Cochrane Database of Systematic Reviews 2009; 4: CD007536.
9. Tieu J, Bain E, Middleton P, Crowther CA. Interconception care for women with a history of gestational diabetes for improving maternal and infant outcomes. Cochrane Database of Systematic Reviews 2013; 6: CD010211.
10. PROSPERO, International prospective register of systematic reviews. [Internet]. York: Centre for Reviews and Dissemination [cited 22 June 2016]. Available from: http://www.crd.york.ac.uk/PROSPERO
11. Cnattingius S, Villamor E. Weight change between successive pregnancies and risks of stillbirth and infant mortality: a nationwide cohort study. Lancet 2016; 387: 558–65.
12. Najafian M, Cheraghi M. Occurrence of Fetal Macrosomia Rate and Its Maternal and Neonatal Complications: A 5-Year Cohort Study. Obstet Gynecol 2012:e353791.
13. Centre for Maternal and Child Enquiries (CMACE) Maternal obesity in the UK: findings from a national project. (2010) London: CMACE.
14. American Diabetes Association. Gestational Diabetes Mellitus. Diabetes Care. 2004;27:88-90.
15. World Health Organisation body mass index (BMI) classification. (Website) Available on: www.who.int/bmi/index.jsp?introPage=intro_3.html. Last accessed 04 Feb 2017.
16. Bogaerts A, Van den Bergh BR, Ameye L, Witters I, Martens E, Timmerman D, Devlieger R. Interpregnancy weight change and risk for adverse perinatal outcome. Obstet Gynaecol 2013;122:999–1009.
17. Cheng C, Bommarito K, Noguchi A, Holcomb W, Leet T. Body mass index change between pregnancies and small for gestational age births. Obstet Gynecol 2004;104(2):286-292.
18. Ehrlich SF, Hedderson MM, Feng J, Davenport ER, Gunderson EP, Ferarra A. Changes in prepregnancy body mass indexes between pregnancies and the risk of gestational diabetes in a second pregnancy. Obstet Gynaecol. 2011;117: 1323–1330.
19. Getahun D, Ananth CV, Peltier MR, Salihu HM, Scorza WE. Changes in prepregnancy body mass index between the first and second pregnancies and risk of large-for-gestational-age birth. Am J Obstet Gynecol 2007;196:e1–e18.

20. Getahun D, Ananth CV, Oyelese Y, Chavez MR, Kirby RS, Smulian JC. Primary preeclampsia in the second pregnancy: effects of changes in prepregnancy body mass index between pregnancies. Obstet Gynecol 2007;110:1319–1325.
21. Jain AP, Gavard JA, Rice JJ, Catanzaro RB, Artal R, Hopkins SA. The impact of interpregnancy weight change on birthweight in obese women. Am J Obstet Gynecol. 2013;208:e1–e7.
22. Whiteman VE, McIntosh C, Rao K, Mbah AK, Salihu HM. Interpregnancy BMI change and risk of primary caesarean delivery. J Obstet Gynaecol 2011;31:589–593.
23. Whiteman VE, Aliyu MH, August EM, McIntosh C, Duan J, Alio AP, Salihu HM. Change in body mass index between pregnancies and risk of gestational and type two diabetes. Arch Obstet Gynaecol 2011;284:235–240.
24. Wallace JM, Bhattacharya S, Campbell DM, Horgan GW. Inter-pregnancy weight change impacts placental weight and is associated with the risk of adverse pregnancy outcomes in the second pregnancy. BMC Pregnancy Childbirth 2014;14: 40.
25. Wallace JM, Bhattacharya S, Campbell DM, Horgan GW. Inter-pregnancy Weight Change and risk of recurrent pregnancy complications. PLoS One 2016;11:e0154812.
26. Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. Lancet 2006;368:1164–1170.
27. Wells G, Shea B, O'Connell J & Roberson J. 2011 The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. (Website) Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Last accessed: 28 Feb 2017
28. Higgins JPT, Altman DG, Gotzshe PC, Juni P, Moher D, Oxman AD. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;3443:d5928.
29. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.
30. Higgins JPT. Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. Int J Epidemiol 2008;37:1158-1160.
31. Higgins JPT, Altman DG, Sterne JAC (2011). Chapter 9: Meta-regression In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 ed. Higgins JPT & Green S. [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org. Last accessed: 14 Mar 2017.
32. Borenstein ML, Hedges V, Higgins JPT, Rothstein HR. (2009) Chapter 20: Meta-regression. In: Introduction to meta-analysis. Chichester: John Wiley & Sons Ltd.
33. Catalano PM. Obesity, Insulin Resistance and Pregnancy Outcome. Reproduction 2010;140:365–371.
34. Pedersen J (1952) Diabetes and pregnancy: blood sugar of newborn infants [PhD thesis], Danish Science Press, Copenhagen (Denmark)
35. Scholl TO, Sowers M, Chen X, Lenders C. Maternal Glucose Concentration Influences Fetal Growth, Gestation, and Pregnancy Complications. Am J Epidemiol 2001;154:514-520.
36. Catalano PM, Hanguel-De Mouzon S. Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic? AJOG 2011;204:479-487.
37. Di Cianni G, Miccoli R, Volpe L. Maternal triglyceride levels and newborn weight in pregnant women with normal glucose tolerance. Diabet Med 2005;22: 21–25.
38. Greene GW, Smiciklas-Wright H, Scholl TO, Karp RJ. Postpartum Weight Change: How Much of Weight Gained in Pregnancy Will Be Lost At Delivery? Obstet Gynecol 1988;71:701-707.
39. McKeown T, Record RG. The influence of weight and height on weight changes associated with pregnancy in Women. J Endocrinol 1957;15:423-429
40. Ock M, Lee S, Jo MW, Lee JY, Kim SH. Assessing Reliability of Medical Record Reviews for the Detection of Hospital Adverse Events. J Prev Med Public Health 2015;48:239–248.
41. Bai J, Wong FWS, Bauman A, Mohsin M. Parity and pregnancy outcomes. AJOG 2002;186:274-278.

42. Ray JG, Vermeulen MJ, Shapiro JL, Kenshole AB. Maternal and neonatal outcomes in pregestational and gestational diabetes mellitus, and the influence of maternal obesity and weight gain: the DEPOSIT study. QJM: An international Journal of Medicine 2001; 94 (7): 347-356.

43. Lau J, Ionnidis J, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. BMJ;2006:333(7568):597-600.

44. Allen J, Hector D. Benefits of breastfeeding. N S W Public Health Bull 2005;16:42-46.

45. Zhu BP. Effect of interpregnancy interval on birth outcomes: findings from three recent US studies. Int J Gynaecol Obstet 2005;89:S25-S33.

46. Brody SC, Harris R, Lohr K. Screening for gestational diabetes: a summary of the evidence for the U.S. Preventive Services Task Force. Obstet Gynecol 2003;101:380-392.

47. National Institute of Health Research (2014) 14/67 Weight management after pregnancy. Available on: njl-admin.nihr.ac.uk/document/download/2007433 Last accessed: 14 Mar 2017

48. IRAS. Supporting Women with Postnatal Weight MAnagemeNt – SWAN Feasibility Trial Protocol. (2016) Available on: njl-admin.nihr.ac.uk/document/download/2007612 Last accessed: 14 Mar 2017

49. Jewell K, Avery A, Barber J, Simpson S. The healthy eating and lifestyle in pregnancy (HELP) feasibility study. BMJ 2014;22:727-736.

50. Sanders J (2016) PRAM. Available on: cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/pram Last accessed: 14 Mar 2017.

51. National Institute for Health and Care Excellence (2010) Weight management before, during and after pregnancy: Public health guideline. Available on: nice.org.uk/guidance/ph27 Last accessed: 14 Mar 2017

FIGURE LEGENDS:

Figure 1: 2009 PRISMA flow diagram showing results of literature search

Figure 2: Forest plot showing change in interpregnancy weight and the risk of large for gestational age births in the subsequent pregnancy, relative to the reference category. (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category -1 to +1 units) Arrow head indicates point of confidence interval truncation at the limit of the graph.

Figure 3: Forest plot showing change in interpregnancy weight and the risk of gestational diabetes mellitus in the subsequent pregnancy, relative to the reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category -1 to +1 units) Arrow head indicates point of confidence interval truncation at the limit of the graph.

Figure 4: Forest plot showing change in interpregnancy weight and the risk of c-section in the subsequent pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category -1 to +1 units)

Figure 5: Forest plot showing change in interpregnancy weight and the risk of SGA in the subsequent pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, increase in BMI defined as > 1 units)

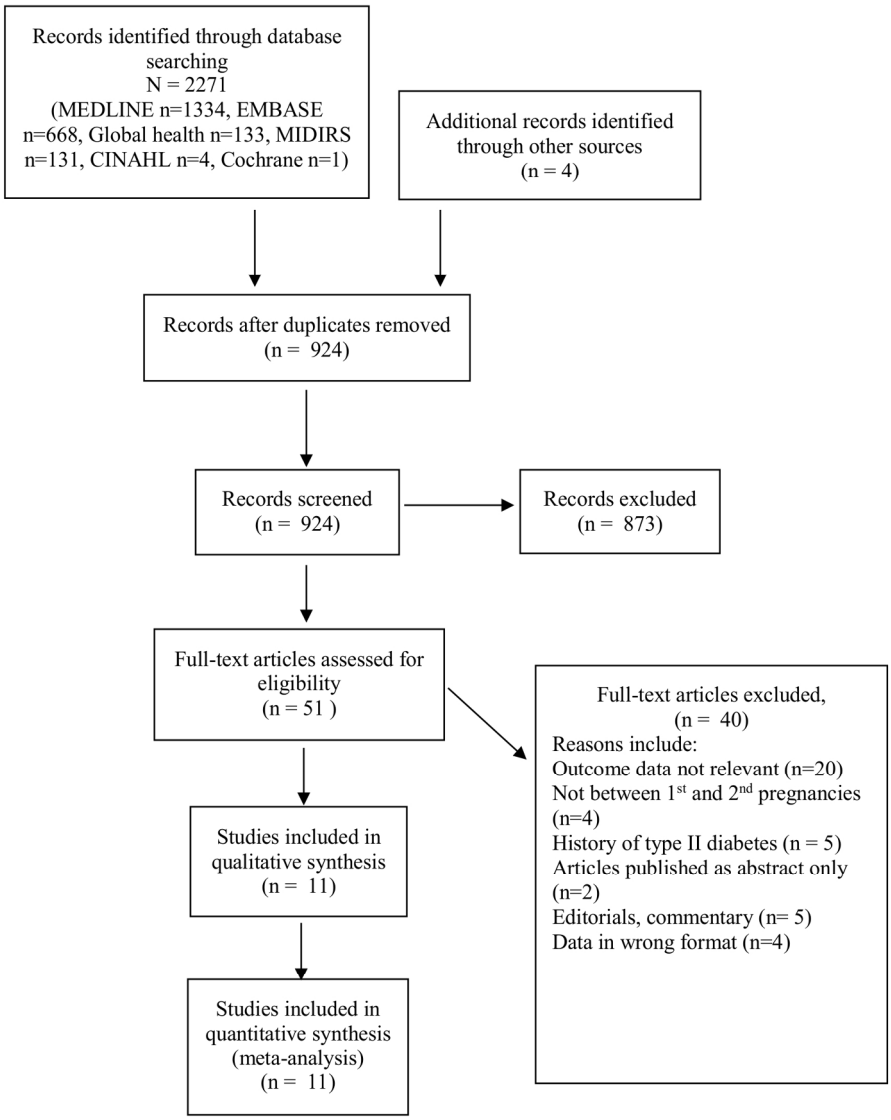

Figure 1: 2009 PRISMA flow diagram showing results of literature search

164x196mm (300 x 300 DPI)

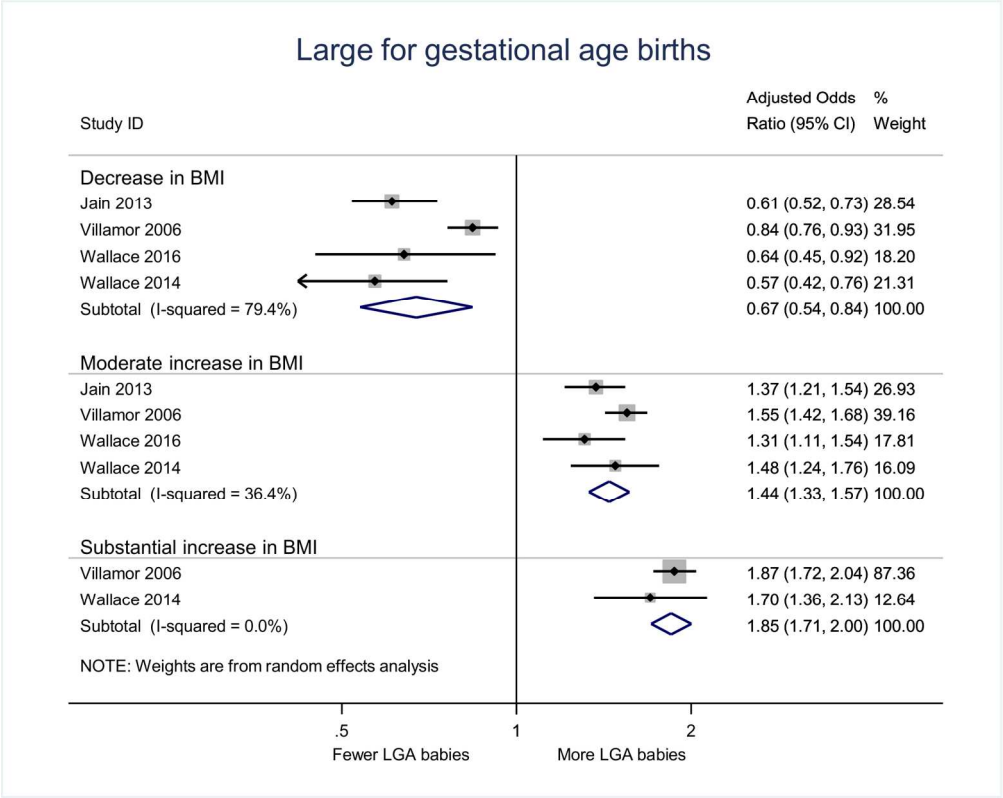

Figure 2: Forest plot showing change in interpregnancy weight and the risk of large for gestational age births in the subsequent pregnancy, relative to the reference category. (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category -1 to +1 units) Arrow head indicates point of confidence interval truncation at the limit of the graph.

156x124mm (300 x 300 DPI)

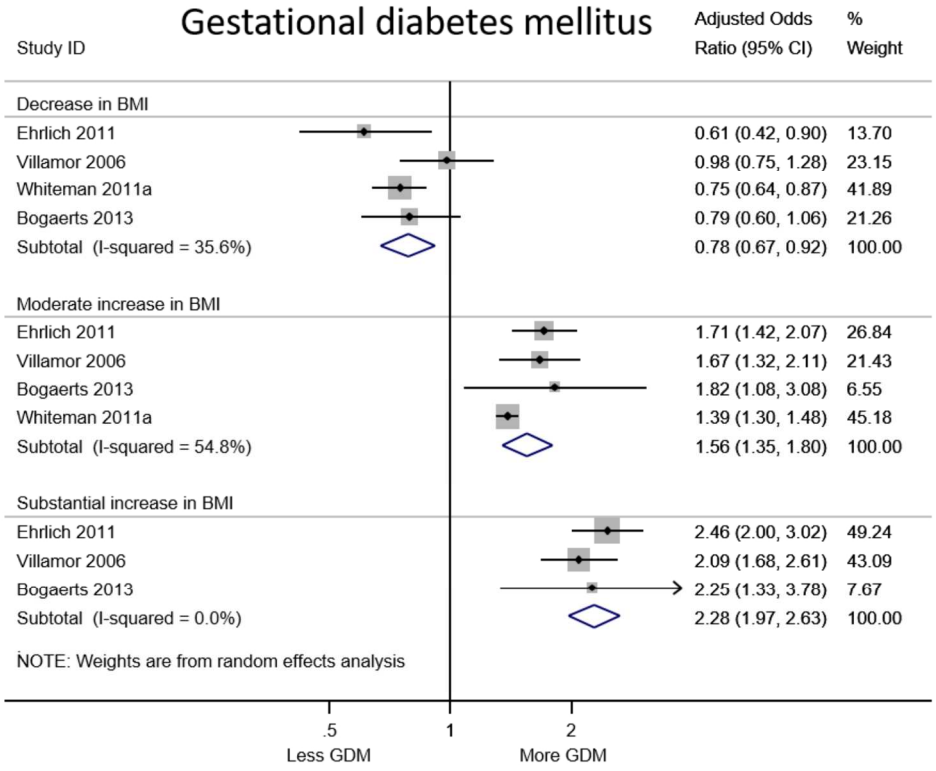

Figure 3: Forest plot showing change in interpregnancy weight and the risk of gestational diabetes mellitus in the subsequent pregnancy, relative to the reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category -1 to +1 units) Arrow head indicates point of confidence interval truncation at the limit of the graph.

157x131mm (300 x 300 DPI)

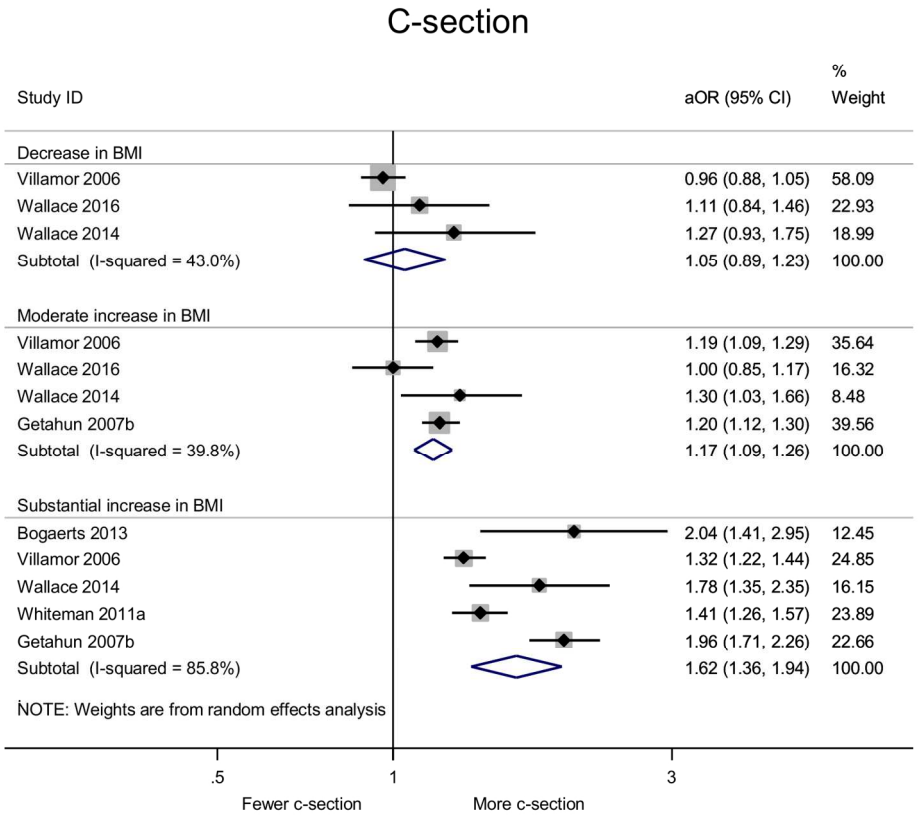

Figure 4: Forest plot showing change in interpregnancy weight and the risk of c-section in the subsequent pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category -1 to +1 units)

151x132mm (300 x 300 DPI)

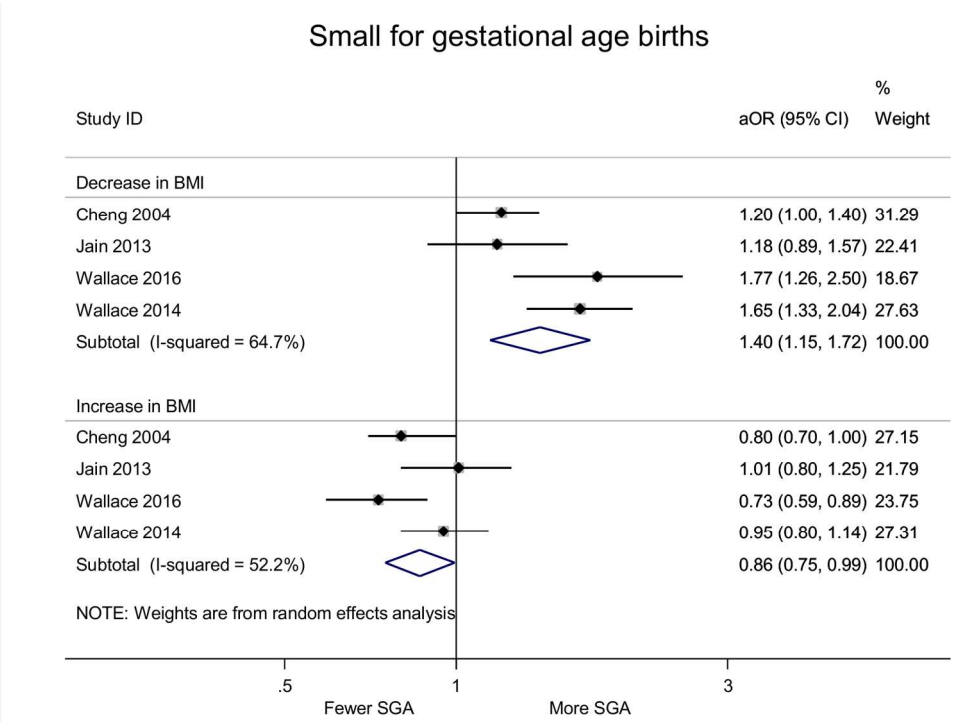

Figure 5: Forest plot showing change in interpregnancy weight and the risk of SGA in the subsequent pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, increase in BMI defined as > 1 units)

157x116mm (300 x 300 DPI)

APPENDIX 1

Table 1: **Criteria for the Newcastle-Ottawa Scale regarding star allocation to assess quality of studies (out of a total of seven stars)**

Criteria	Acceptable (star awarded):	Unacceptable (star not awarded):
Representativeness of exposed cohort	Population-based	Hospital-based
Selection of non-exposed cohort	Same setting as exposed cohort	Different setting from exposed cohort
Ascertainment of exposure	Secure records or directly measured	Self-reported information
Comparability	Excluded or adjusted for prior outcome in analysis	No exclusion of prior outcome in previous pregnancy
	Adjusted for age, race, smoking and interpregnancy interval	Did not adjust for age, race, smoking and interpregnancy interval
Outcome of interest	Secure records or directly measured	Self-reported information
Adequacy of follow-up	Adjusted for missing data or follow-up > 1 month.	No statement regarding missing data. No follow-up after birth.

Table 2: Quality assessment of studies using a modified Newcastle-Ottawa scale for assessing studies in the systematic review of interpregnancy weight change and pregnancy outcome

Study ID	Selection			Comparability*	Outcome		Total (7⋆)
	Representativeness of exposed cohort (⋆)	Selection of non-exposed cohort (⋆)	Ascertainment of exposure (⋆)	(⋆⋆)	Assessment of outcome (⋆)	Adequacy of follow up (⋆)	
Bogaerts 2013	⋆	⋆	-	⋆⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Cheng 2004	⋆	⋆	-	⋆⋆	⋆	⋆	⋆⋆⋆⋆⋆⋆ (6)
Ehrlich 2011	-	⋆	⋆	⋆⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Getahun 2007a	⋆	⋆	-	⋆ -	⋆	-	⋆⋆⋆⋆ (4)
Getahun 2007b	⋆	⋆	-	⋆⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Jain 2013	⋆	⋆	-	⋆⋆	⋆	⋆	⋆⋆⋆⋆⋆⋆ (6)
Villamor 2006	⋆	⋆	⋆	⋆⋆	⋆	-	⋆⋆⋆⋆⋆⋆ (6)
Wallace 2014	-	⋆	⋆	⋆⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Wallace 2016	⋆	⋆	⋆	- ⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Whiteman 2011a	⋆	⋆	-	⋆⋆	⋆	⋆	⋆⋆⋆⋆⋆⋆ (6)
Whiteman 2011b	⋆	⋆	-	⋆⋆	⋆	⋆	⋆⋆⋆⋆⋆⋆ (6)

***** Comparability assessed as the following: one star rewarded if study excluded or adjusted for outcome in first pregnancy, another star rewarded if study adjusted for age, race, smoking and interpregnancy interval

Table 3: Risk of bias assessment (modified from Cochrane Tool to Assess Risk of Bias in Cohort Studies and EPOC Data Collection Form)[29]

Study ID	Allocation concealment (selection bias)	Assessment of exposure (self-report)	Outcome of interest present at beginning	Incomplete data	Selective reporting (reporting bias)	Total score*
Bogaerts 2013	+	-	+	+	-	3
Cheng 2004	+	-	+	+	+	4
Ehrlich 2011	-	+	+	?	+	3
Getahun 2007a	+	-	?	?	+	2
Getahun 2007b	+	-	+	?	+	3
Jain 2013	+	-	+	+	+	4
Villamor 2006	+	+	+	?	+	4
Wallace 2014	-	+	+	?	+	3
Wallace 2016	+	+	-	?	+	3
Whiteman 2011a	+	-	+	+	+	4
Whiteman 2011b	+	-	+	+	+	4

*Total score: points awarded based on number of "+" or low risk of bias
+ = Low risk of bias, ? = Unclear risk of bias, - = High risk of bias

APPENDIX 2

Table 1: Overall statistical significance of effect size = 1

Outcome	Change in BMI	Z value	P-value
LGA	Decrease	z= 7.02	p = 0.000
	Moderate increase	z= 12.47	p = 0.000
	Substantial increase	z= 15.09	p = 0.000
Macrosomia	Decrease	z= 2.46	p = 0.014
	Moderate increase	z= 3.76	p = 0.000
	Substantial increase	z= 1.72	p = 0.086
GDM	Decrease	z= 3.03	p = 0.002
	Moderate increase	z= 6.02	p = 0.000
	Substantial increase	z= 11.16	p = 0.000
C-section	Decrease	z= 0.55	p = 0.579
	Moderate increase	z= 4.11	p = 0.000
	Substantial increase	z= 5.30	p = 0.000
SGA	Decrease	z= 3.27	p = 0.001
	Increase	z= 2.05	p = 0.041

Table 2: Overall statistical significant of effect size = 1 in subgroups of women with a BMI before pregnancy of < 25 or ≥ 25

Outcome	Change in BMI	Z value	P-value
LGA BMI < 25	Decrease	z= 3.18	p = 0.001
	Moderate increase	z= 18.27	p = 0.000
	Substantial increase	z= 17.7	p = 0.000
LGA BMI ≥ 25	Decrease	z= 2.94	p = 0.003
	Moderate increase	z= 1.64	p = 0.102
	Substantial increase	z= 4.87	p = 0.000
GDM BMI < 25	Decrease	z= 2.11	p = 0.035
	Moderate increase	z= 4.03	p = 0.000
	Substantial increase	z= 3.83	p = 0.000
GDM BMI ≥ 25	Decrease	z= 2.42	p = 0.016
	Moderate increase	z= 13.75	p = 0.000
	Substantial increase	z= 18.11	p = 0.000
C-section BMI < 25	Decrease	z= 0.82	p = 0.415
	Moderate increase	z= 5.06	p = 0.000
	Substantial increase	z= 4.33	p = 0.000
C-section BMI ≥ 25	Decrease	z= 3.05	p = 0.002
	Moderate increase	z= 2.10	p = 0.036
	Substantial increase	z= 1.37	p = 0.170

APPENDIX 3

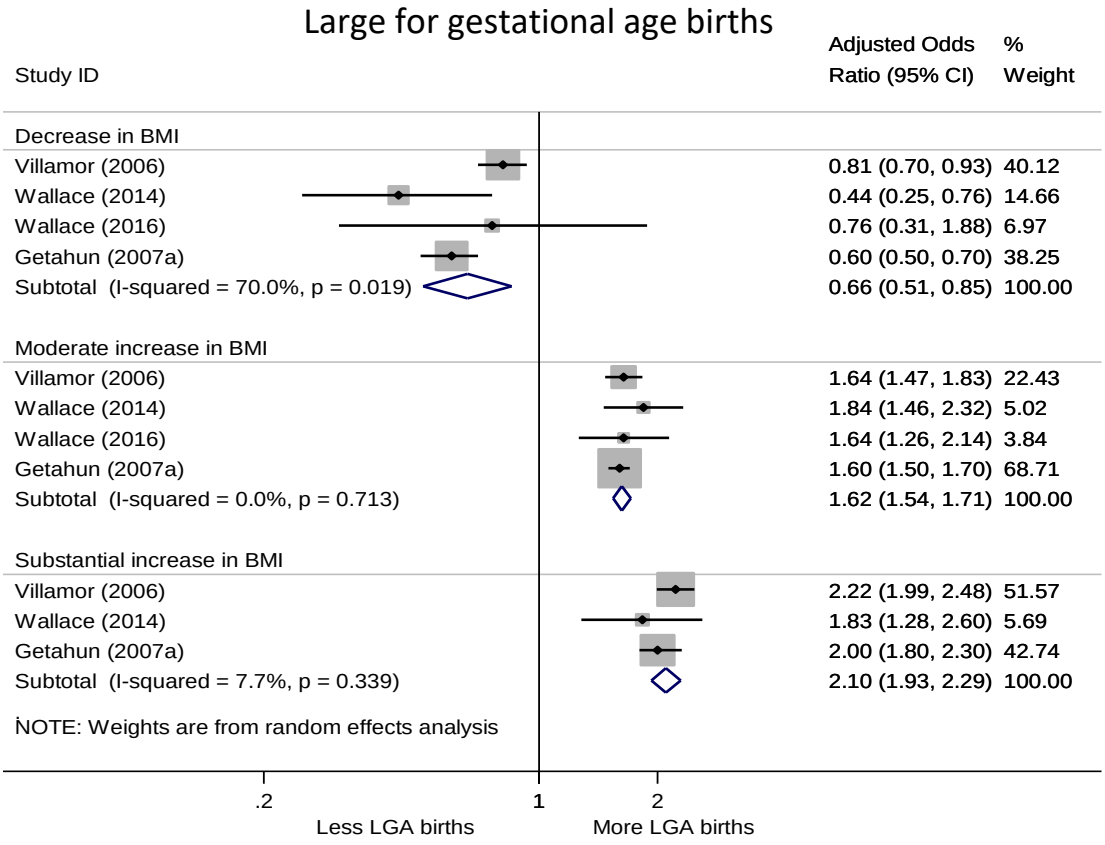

Figure 1: Forest plot showing change in interpregnancy weight and the risk of large for gestational age births in the subsequent pregnancy for women with normal BMI (< 25) at the beginning of first pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category -1 to +1 units)

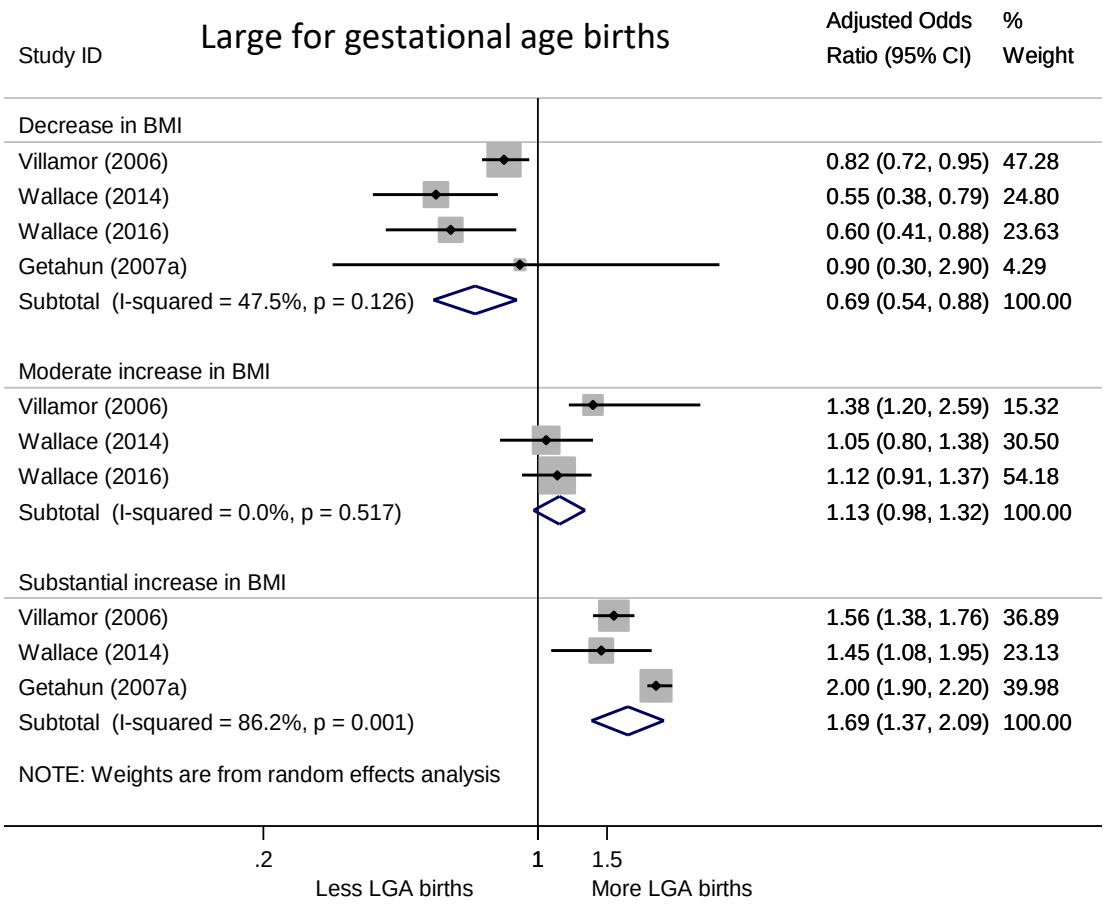

Figure 2: Forest plot showing change in interpregnancy weight and the risk of large for gestational age births in the subsequent pregnancy for women with overweight/obese BMI (≥ 25) at the beginning of first pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category -1 to +1 units)

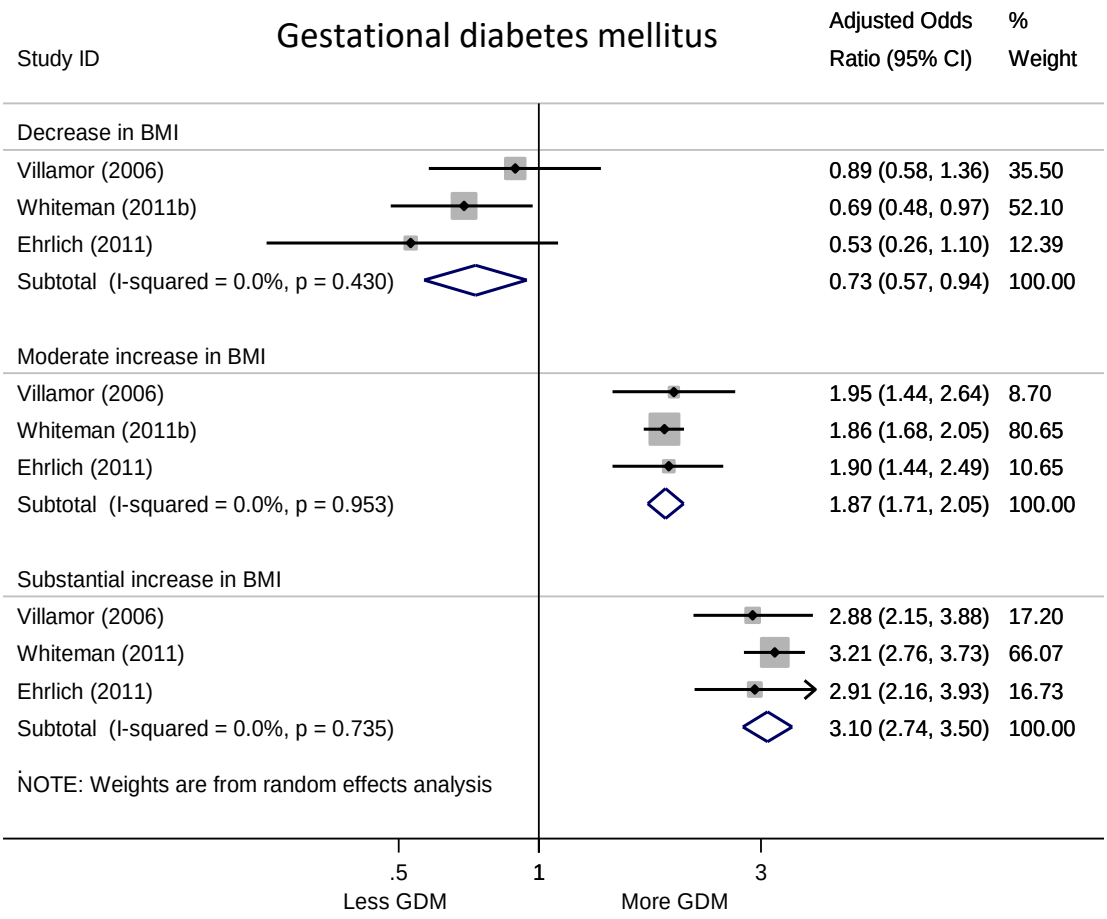

Figure 3: Forest plot showing change in interpregnancy weight and the risk of gestational diabetes mellitus in the subsequent pregnancy for women with normal BMI (< 25) at the beginning of first pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category -1 to +1 units)

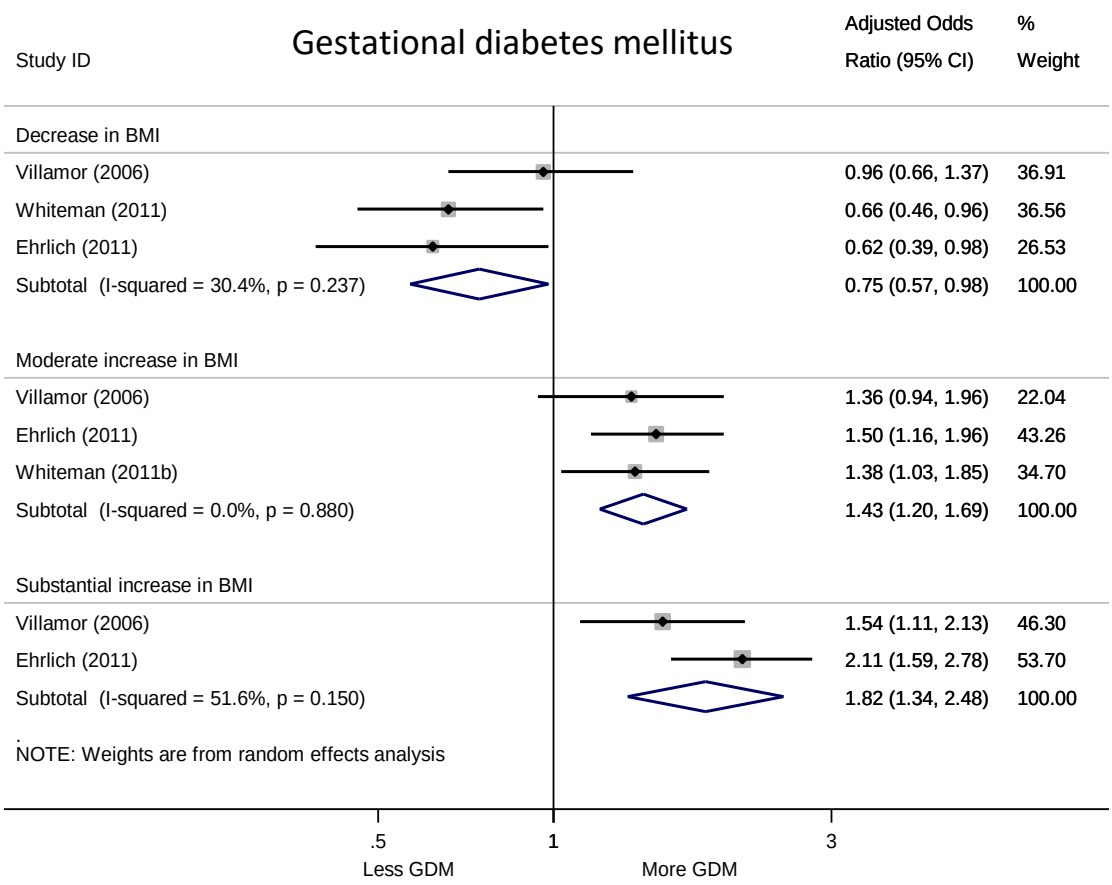

Figure 4: Forest plot showing change in interpregnancy weight and the risk of gestational diabetes mellitus in the subsequent pregnancy for women with overweight/obese BMI (≥ 25) at the beginning of first pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category -1 to +1 units)

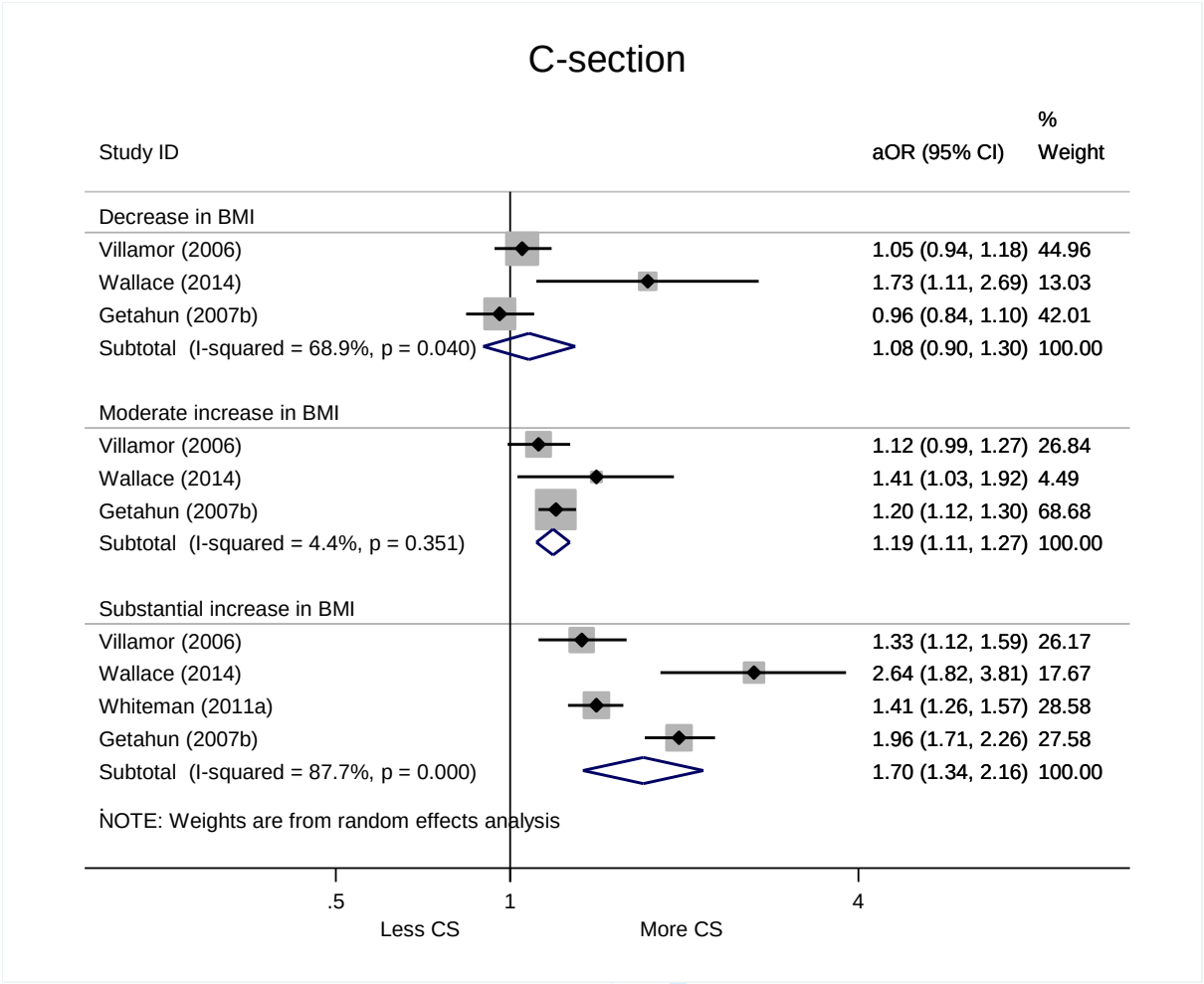

Figure 5: Forest plot showing change in interpregnancy weight and the risk of C-section in the subsequent pregnancy for women with normal BMI (< 25) at the beginning of first pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category -1 to +1 units)

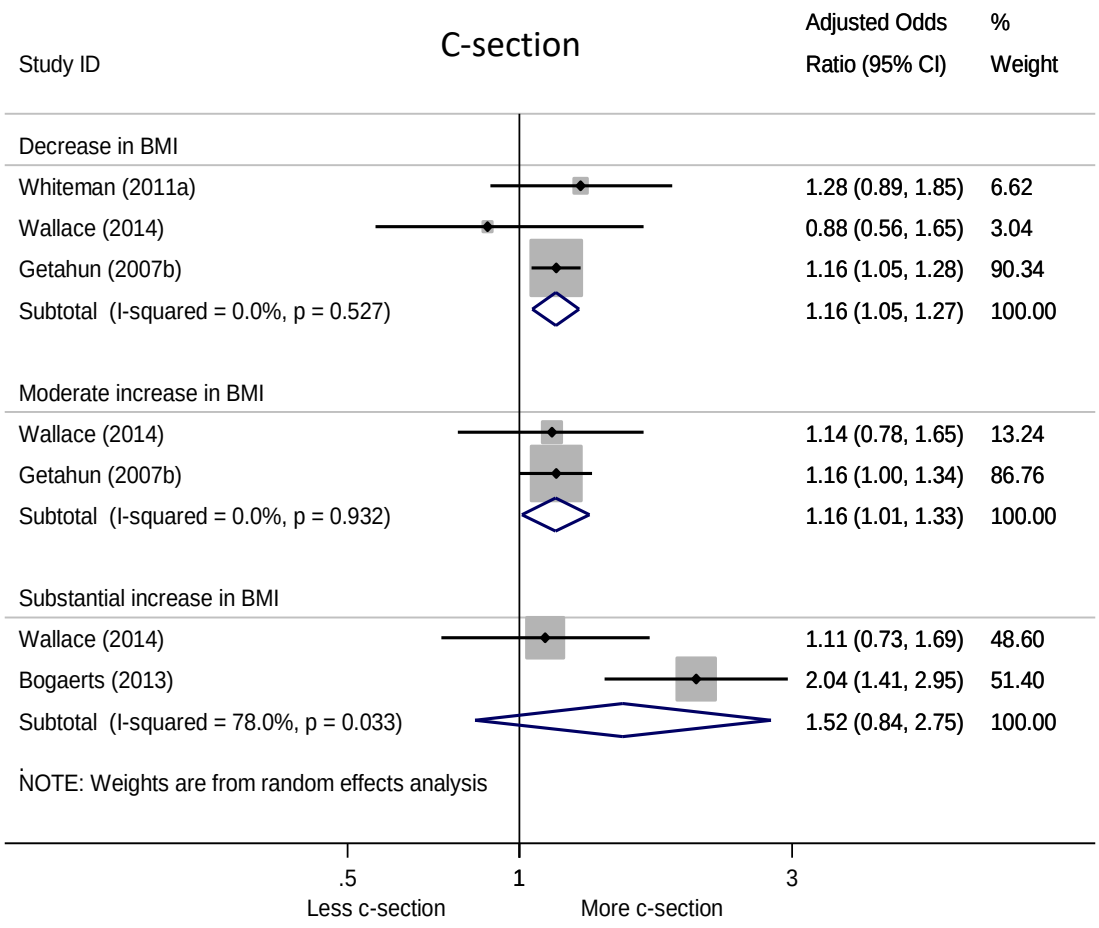

Figure 6: Forest plot showing change in interpregnancy weight and the risk of C-section in the subsequent pregnancy for women with overweight/obese BMI (≥ 25) at the beginning of first pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category -1 to +1 units)

APPENDIX 4

Table 1: Results after sensitivity analysis for the effect of interpregnancy BMI change on large for gestational age births, in women with a prepregnancy BMI of < 25 and ≥ 25. (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

Prepregnancy BMI	BMI change	Number of studies	aOR (05% CI)	I^2	p-value
< 25	Decrease	3	0.674 (0.447-1.016)	54.00%	0.114
	Moderate increase	3	1.671 (1.523-1.833)	0.00%	0.672
	Substantial increase	2	2.176 (1.938-2.443)	4.00%	0.307
≥ 25	Decrease	3	0.676 (0.511-0.895)	64.50%	0.06
	Moderate increase	3	1.134 (0.975-1.319)	0.00%	0.517
	Substantial increase	2	1.544 (1.379-1.727)	0.00%	0.654

Appendix 5 : PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**2**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**3**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**3**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**4**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**4**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**4**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**4**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**4**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**4-5**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**5**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**5**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**4**
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**5**

Section/topic	#	Checklist item	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**5**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**5**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**6**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**7-8**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**Appendix 1**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**9**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**9**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**Appendix 1**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**9**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**10**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**11**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**12**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**13**

Appendix 5 : PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**2**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**3**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**3**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**4**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**4**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**4**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**4**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**4**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**4-5**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**5**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**5**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**4**
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**5**

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**5**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**5**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**6**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**7-8**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**Appendix 1**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**9**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**9**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**Appendix 1**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**9**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**10**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**11**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**12**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**13**

BMJ Open

Interpregnancy Weight Change and Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018778.R3
Article Type:	Research
Date Submitted by the Author:	10-Apr-2018
Complete List of Authors:	Oteng-Ntim, Eugene ; London School of Hygiene and Tropical Medicine Mononen, Sofia; King's College, London, Department of Women and Children's Health Sawicki, Olga; London School of Hygiene and Tropical Medicine Seed, Paul; Kings College, London, Department of Women and Children's Health Bick, Debra; Kings College London, Department of Women and Children's Health Poston, Lucilla; Kings College, London, Department of Women and Children's Health
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	BMI, Interpregnancy, Maternal medicine < OBSTETRICS

Interpregnancy Weight Change and Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis

Eugene Oteng-Ntim, Sofia Mononen, Olga Sawicki, Paul T Seed, Debra Bick, Lucilla Poston

London School of Hygiene and Tropical Medicine, London, UK

Eugene Oteng-Ntim PhD
Associate Professor Epidemiology and Population Health
Consultant Obstetrician,

Olga Sawicki MD, MSc
Senior Scientist in UNAIDS

Department of Women and Children's Health, King's College London, St. Thomas' Hospital, London, UK

Sofia Mononen
MBBS BSc student

Paul T Seed MSc
Senior Lecturer in Medical Statistics

Prof Debra Bick PhD
Professor of Evidence Based Midwifery

Prof Lucilla Poston PhD
Tommy's Campaign Professor of Maternal and Fetal Health, Head of Division of Women's Health

Correspondence to: Dr Eugene Oteng-Ntim, Department of Women's Health, Guy's and St Thomas' National Health Service Foundation Trust, London SE1 7EH, UK, eugene.oteng-ntim@gstt.nhs.uk

ABSTRACT

Objectives: To evaluate the effect of interpregnancy BMI change on pregnancy outcomes, including large-for-gestational-age babies (LGA), small-for-gestational-age babies (SGA), macrosomia, gestational diabetes mellitus (GDM), and caesarean section.

Design: Systematic review and meta-analysis of observational cohort studies

Data sources: Literature searches were performed across Cochrane, MEDLINE, EMBASE, CINAHL, Global Health and MIDIRS databases.

Study selection: Observational cohort studies with participants parity 0 to 1.

Main outcome measures: Adjusted odds ratios (aOR) with 95% confidence intervals were used to evaluate the association between interpregnancy BMI change on five outcomes.

Results: 925,065 women with singleton births from parity 0 to 1 were included in the meta-analysis of eleven studies selected from 924 identified studies. A substantial increase in interpregnancy BMI (> 3 BMI units) was associated with an increased risk of LGA (aOR=1.85, 95% CI 1.71-2.00, p<0.001), GDM (aOR=2.28, 1.97-2.63, p<0.001), macrosomia (aOR=1.54, 95% CI 0.939-2.505) and c-section (aOR=1.72, 1.32-2.24, p<0.001) compared with the reference category, and a decreased risk of SGA (aOR=0.83 95% CI 0.70-0.99, p=0.044). An interpregnancy BMI decrease was associated with a decreased risk of LGA births (aOR=0.70 95% CI 0.55-0.90,p<0.001), and GDM (aOR=0.80 95% CI 0.62-1.03), and an increased risk of SGA (aOR=1.31 95% CI 1.06-1.63, p=0.014). Women with a normal BMI (<25) at first pregnancy who have a substantial increase in BMI between pregnancies had a higher risk of LGA (aOR=2.10, 1.93-2.29) and GDM (aOR=3.10, 2.74-3.50) when compared to a reference than women with a BMI≥25 at first pregnancy.

Conclusions: Gaining weight between pregnancies increases risk of developing GDM, CS and LGA, and reduces risk of SGA in the subsequent pregnancy. Losing weight between pregnancies reduces risk of GDM and LGA and increases risk of SGA. Weight stability between first and second pregnancy is advised in order to reduce risk of adverse outcomes.

Registration: PROSPERO CRD42016041299

Strengths and limitations of the study

- We believe this to be the first meta-analysis completed on the topic of interpregnancy weight change and its effect on five adverse pregnancy outcomes.
- A large sample size of 925,065 women was collected from eleven well-adjusted population-based observational studies, with two methods used to assess the quality of the studies.
- Sensitivity analysis was conducted to remove low quality research, which did not change the direction of effect for any outcome.
- Limitations included limited generalisability, as the research was conducted in high-income countries and only in women from parity 0 to 1.
- Further, high heterogeneity persisted after sensitivity analysis, and additional confounders (such as breastfeeding) could affect the results.

INTRODUCTION

The associations between high pregravid body mass index (BMI) and maternal and neonatal complications are well established;[1] complications include gestational diabetes mellitus (GDM), caesarean section (CS), preeclampsia, macrosomia, prematurity, and stillbirth.[2] These outcomes are of public health importance because they add to the disease burden of women and their infants thereby increasing health care costs.[3] Mirroring the trend of the global obesity epidemic (more than half of all women of reproductive age in the UK are overweight or obese),[4] the prevalence of all these pregnancy complications has risen, as has the focus on maternal weight management as a means to improve the health of women and their children.

Previous studies have investigated the effect and impact of increased weight on adverse outcomes at all stages of the periconceptional period.[5] Lifestyle and medical interventions during pregnancy have shown little effect on pregnancy outcomes.[6] In the meantime, interpregnancy care is aimed at optimising outcomes of women and their future babies.[7] But standards are lacking[8] and, owing to the paucity of literature, systematic reviews and meta-analysis, any effect of interpregnancy care on pregnancy outcomes remains nascent.[8-10]

Despite a plausible rationale for weight management as part of interpregnancy planning, a knowledge gap exists amongst healthcare providers and women of reproductive age of the impact of weight change between pregnancies. Interpregnancy weight change is defined as the difference in BMI between first and second pregnancy recorded at the first antenatal visit.[11] Whilst the number of relevant studies has expanded in recent years, no meta-analysis has been attempted. The aim of this meta-analysis was to address this gap by examining the association between interpregnancy weight change and the most prevalent associated adverse pregnancy outcomes: GDM, CS, LGA and SGA babies in the next pregnancy (see table 1 for definitions). Where possible, the data were divided according to maternal BMI <25 kg/m^2 and BMI ≥25 kg/m^2, in order to address effects of interpregnancy weight change in the overweight/obese population compared to women with a normal BMI. Only the first two successive pregnancies were assessed in order to minimise confounding due to any effects of parity on pregnancy outcome.

Table 1: **Definitions of maternal and foetal outcomes used throughout this review**

Outcome	*Definition*
Large for gestational age (LGA)	A baby with birth weight ≥90th percentile of all babies with same gestational age[2]
Small for gestational age (SGA)	A baby with birth weight <10th percentile of all babies with same gestational age[2]
Macrosomia	Birth weight of >4000g[12]
Caesarean section	Surgical incision into abdominal and uterine wall to achieve delivery of the baby[13] Only emergency CS was considered in this study.
Gestational diabetes mellitus (GDM)	Any degree of glucose intolerance with onset or first recognition during pregnancy[14]

Table 2: Search strategy for MEDLINE

1	exp birth intervals/
2	(interpregnan* or inter-pregnan* or (birth adj interval) or (between adj pregnan*) or (successive adj pregnan*) or interbirth or (pregnan* adj spacing) or (pregnan* adj interval) or (birth adj spacing) or interdelivery or (consecutive adj pregnan*) or (following adj pregnanc*) or (subsequent adj pregnan*)).mp.
3	1 or 2
4	((body adj weight) or body mass index or BMI or (weight adj change) or (weight adj los*) or (weight adj decrease) or (weight adj gain*) or (weight adj increase) or (BMI adj change) or (body adj mass adj index) or (body adj weight adj change)).mp.
5	((pregnancy adj complication) or (f?etal adj outcome) or (pregnancy adj outcome) or (adverse adj outcome) or macrosomia or large for gestational age or LGA or large-for-gestational-age or (birth adj weight) or SGA or small for gestational age or small-for-gestational-age or GDM or (gestational adj diabetes) or c-section or (c?esarean adj section).mp.
6	3 and 4 and 5
7	Limit 6 to humans

METHODS

Protocol and registration

The study was registered in PROSPERO International prospective register of systematic reviews (CRD42016041299). The criteria outlined in the PRISMA statement and the MOOSE checklist was adhered to.

Information sources

Electronic databases including CINAHL, EMBASE, MEDLINE, the Cochrane Database of Systematic Reviews, MIDIRS and Global Health were searched from January 1990 to January 2017. Searches were limited to studies in humans. There were no language constraints. In addition, references from bibliographies and citations were manually searched. A grey literature search was run until January 1, 2017 across the following clinical trials registries: TRIP Database, EThOS, WHO International Clinical Trials Registry Platform Search Portal and the EU Clinical Trials Register.

Search strategy

A search strategy was developed for MEDLINE (see table 2) and adapted for other databases. The following combination of MeSH terms and free text were used: interpregnancy, prepregnancy, weight gain, weight loss, neonatal outcomes, and pregnancy complications.

Outcome measures

Five of the most prevalent adverse outcomes were chosen as outcomes of interest for this review. These included LGA, SGA, macrosomia, c-section (CS) and GDM (defined in table 1). Gender-specific birth weight charts were used in the research for LGA and SGA birth weights. It should be noted that throughout this paper, BMI will be referred to in groups according to the WHO and NICE BMI classifications.[15]

Study selection

Observational studies such as cohort and case-control studies were included, with studies limited to humans. Only singleton births from parity 0 to 1 were included. Studies that were restricted to women with previous

diabetes diagnoses were excluded, as were studies published as conference abstracts, reviews, pharmacological or surgical interventions for weight loss, case reports or unpublished trials. Citations found through database searches and other searches such as browsing bibliographies were combined and duplicates excluded.

Data collection and extraction

The Cochrane Good Practice Data Extraction Form was used for extracting relevant data of each study. Raw data was collected where available or calculated from the information given. Adjusted odds ratios and confidence intervals were extracted from all papers. Additional information collected from studies included: first author's name and year of publication, study design, setting, study period, sample size, outcomes, inclusion/exclusion criteria, quality assessment and population demographics and factors that each study adjusted for (including age, race, socioeconomic status, interpregnancy interval, previous maternal disease, gestational weight gain and education level).

To study whether association between change in body weight and adverse outcomes differed, study groups were classified as "substantial increase in BMI", "moderate increase in BMI" and "decrease in BMI". These groups were defined as BMI increase of more than 3 units (substantial increase), BMI increase between 1 and 3 units (moderate increase) and BMI decrease more than 1 units (decrease). If an outcome had small number of studies, substantial increase and moderate increase were combined as "increase in BMI". In studies that reported results based on WHO classification, women who changed from normal weight to underweight were considered as part of the BMI decrease category, and weight change from normal to obese represented a substantial increase in BMI. These studies were used as part of subgroup analyses (initial BMI >25 "overweight/obese" or BMI < 25 "normal") and converted into substantial (normal to obese), moderate (normal to overweight) and decrease in BMI groups (normal to underweight) respectively.

Interpregnancy weight change was defined as the prepregnancy BMI before first pregnancy to the prepregnancy BMI before second pregnancy. For each outcome, the association of BMI change on adverse pregnancy outcome was compared to the reference category, which was defined as women who remained within their BMI category or their BMI changed by up to 2 units in either direction.

Two investigators (SM, OS) independently performed the literature search, assessed the eligibility and quality of the retrieved papers, and performed the data extraction. The two authors compared the results and disagreements were resolved by a third reviewer (EO).

Risk of bias assessment

To assess the quality of the studies, a modified Newcastle-Ottawa scale and a Cochrane analysis of bias were performed. Sensitivity analysis was performed by removing studies with a NOS score (≤4 stars) or a high level of bias (<3 points) according to the Cochrane analysis.

Statistical analysis

Forest plots were made for each outcome to assess overall effect size and heterogeneity using Stata SE 14 (StataCorp, College Station, Texas, USA). Random effects model was used to account for variability across studies. Study weight was calculated using the inverse variance method. Data was pooled and heterogeneity assessed with the I^2 statistic, with a high heterogeneity defined as being over 50%. Results were considered statistically significant if p was less than 0.05. Sensitivity analysis was performed by removing low quality studies. Analysis was then repeated and results compared.

Role of funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Patient and Public Involvement

No patients were involved in setting the research question or the outcome measures, and no patients were involved in developing plans for design or implementation of the study. Further, no patients were asked to advice on interpretation or writing up of results. Since this meta-analysis used aggregated data from previous trials, it is unable to disseminate the results of the research to study participants directly.

RESULTS

Literature search results

Results from the literature search came back with eleven studies to be included in the qualitative synthesis. The 2009 PRISMA flow diagram can be seen in figure 1, showing the process of study selection.

Study characteristics

Study characteristics can be found in table 3. Out of the studies, one study was from Belgium[16], seven were from USA[17,18,19,20,21,22,23], two from Scotland[24,25], and one from Sweden[26]. Four papers studied GDM, five papers studied LGA, four papers studied SGA, one paper studied macrosomia, and six papers studied c-section (table 3). All studies presented their data in adjusted odds ratios (aOR). Seven out of the eleven studies used self-reports to record prepregnancy weight and height. All studies adjusted for confounding variables such as age, race, education and marital status with most studies also adjusting for interpregnancy interval, smoking, socioeconomic status, alcohol use, country of birth and maternal illness. About half of the prospective studies were community-based, using data found from national or state databases whilst other studies used hospital data.

Data quality

Data quality was assessed using a modified Newcastle-Ottawa scale[27] as well as a Cochrane tool of assessing bias in studies[28]. The criteria for allocating stars (out of a total of seven stars) awarded to each study according to this NOS criteria can be found in appendix 1 table 1. The results of this data quality assessment can be seen in appendix 1, tables 2 and 3. The exposed cohort was defined as women with a change in interpregnancy BMI, whilst the non-exposed cohort was defined as women who remained within their original BMI category or their BMI changed by up to 2 units in either direction.. Despite authors attempting to adjust for the missing data, only five studies assessed the problem of missing data and analysed if this missing data was significant. One study[16] did not report data unless it was statistically significant, giving rise to a possible high risk of reporting bias. Self-reported assessment of exposure as well as incomplete data are the two greatest sources of bias in the studies. The total score shown in appendix 1, table 3 allows for comparison of Cochrane analysis of bias and NOS. These two assessments show good agreement; good quality studies tended to have a lower risk of bias.

Table 3: Study characteristics of studies chosen for meta-analysis and review of inter-pregnancy weight change and adverse pregnancy outcomes

Study ID	Study date	Sample size	Study setting	Study type	Relevant outcomes	BMI change measured in	Confounders adjusted for	Self-reported weight/ height	Limitations
Bogaerts[16]	2013	7,897	Belgium	Population-based retrospective cohort	GDM, c-section, macrosomia	Units (-1, -1 to 1, 2, >2, >3)	Pre-pregnancy BMI, age, marital status, alcohol use, inter-pregnancy interval and gestational weight gain	Yes	No information on prior diabetes, hypertension, smoking, family history, diet, physical activity or stress, education or ethnicity, small sample. Non-significant data excluded.
Cheng[17]	2004	14,114	USA	Population-based case-control	SGA	Increase/Decrease	Pre-pregnancy BMI, age, race, marital status, education, prenatal care	Yes	No information on gestational weight gain, physical activity, diet.
Ehrlich[18]	2011	22,351	USA	Population-based retrospective cohort	GDM	Units (>-2, -1 to -2, 0-1, 1-1.9)	Age, race-ethnicity, place of birth, GDM and BMI in the first pregnancy, gestational age at the weight measurements, and time interval between pregnancies.	No	No information on gestational weight gain, pre-pregnancy BMI, family history, physical activity, diet, breastfeeding.
Getahun[19]	2007a	146,227	USA	Population-based retrospective cohort	LGA	Groups (underweight, normal, overweight, obese)	Pre-pregnancy BMI, age, race, education, marital status, pre-natal care, smoking, inter-pregnancy interval	Yes	No information on family history, diet, physical activity or stress
Getahun[20]	2007b	113,789	USA	Population-based retrospective cohort	C-section	Groups (underweight, normal, overweight, obese)	Pre-pregnancy BMI, age, race, education, marital status, pre-natal care, smoking, inter-pregnancy interval	Yes	No information on family history, diet, physical activity or stress
Jain[21]	2013	10,444	USA	Population-based retrospective cohort	LGA, SGA	Weight loss/weight gain	Pre-pregnancy BMI, age, race, ethnicity, marital status, socioeconomic status, education, inter-pregnancy interval	Yes	No information on family history, diet, physical activity or stress

Study ID	Study date	Sample size	Study setting	Study type	Relevant outcomes	BMI change measured in	Confounders adjusted for	Self-reported weight/ height	Limitations
Villamor[26]	2006	207,534	Sweden	Population-based retrospective cohort	GDM, LGA, c-section,	Units (<-1, -1 to 1, 1 to <2, 2 to <3, >3)	Baseline BMI (at first pregnancy), height, interpregnancy interval, age, country of origin, years of education, year of delivery, and smoking.	No	No information for family history, diet, physical activity or stress.
Wallace[24]	2014	12,740	Scotland	Population-based retrospective cohort	LGA,SGA, c-section	Units, >-1, -1 to +1,1 to <3 and >3	Baseline BMI (at first pregnancy), age, smoking, gestational age, baby gender, year of delivery at first pregnancy, height, inter-pregnancy interval	No	Low event rate, no information for family history, diet, physical activity or stress
Wallace[25]	2016	24,450	Scotland	Population-based retrospective cohort	LGA, SGA, c-section	Units, >-2, -2 to +2 and >2	Baseline BMI (at first pregnancy), age, smoking, gestational age, baby gender, year of delivery at first pregnancy, height, inter-pregnancy interval	No	Low event rate, no information for family history, diet, physical activity or stress
Whiteman[22]	2011a	100,828	USA	Population-based retrospective cohort	C-section	Groups (underweight, normal, overweight, obese)	Pre-pregnancy BMI, age, race, education, marital status, year of birth, common obstetric complications, prenatal care, interpregnancy interval, smoking, alcohol	Yes	Use of vital statistics data, no information for family history, diet, physical activity or stress
Whiteman[23]	2011b	232,272	USA	Population-based retrospective cohort	GDM	Groups (underweight, normal, overweight, obese)	Pre-pregnancy BMI, age, race, education, marital status, year of birth, common obstetric complications, prenatal care, interpregnancy interval, smoking, alcohol	Yes	Inability to separate GDM from type 2 diabetes, no information for family history, diet, physical activity or stress

Outcomes

A decrease in BMI (>1 BMI unit) was associated with a 33% reduction in LGA births (aOR 0.70 (95% CI 0.55-0.90), I^2=82.0%), whilst a moderate increase in BMI is associated with a 43% higher risk of LGA birth compared with the reference category (aOR 1.43 (95% CI 1.29-1.59), I^2=57.4%). A significant increase in BMI, defined as being an increase of over 3 units, had the highest risk of LGA birth (aOR=1.85 (95% CI 1.71-2.00), I^2=0%) (figure 2). Z-values and p-values for these results (appendix 2 table 1) show that all three pooled estimates were statistically significant (p<0.05).

Only one study included macrosomia as an outcome[16]. Their results showed that decrease in BMI had a reduced risk of macrosomia, aOR=0.5 (0.35-0.71), with a substantial increase in BMI associated with a higher risk of macrosomia (aOR=1.537(0.939-2.505). It should be noted that this paper also reported data for low birth weight (<2500g) and found that a decrease in BMI >-1 unit was associated with aOR 2.22 (1.41-3.51).

A decrease in BMI (>1 BMI unit) resulted in a decreased risk of GDM (aOR 0.80 (95% CI 0.62-1.03), I^2=51.1%). A moderate increase in BMI was associated with a 56% increased risk of GDM (aOR 1.70 (95% CI 1.48-1.96), I^2=0.0%). A substantial increase in BMI (more than 3 units) was similarly associated with a high risk of GDM (aOR 2.28 (95% CI 1.97-2.63), I^2=0.0%) (figure 3). P-values for these pooled results were statistically significant for moderate (p<0.001) and substantial increase in BMI (p<0.001) and risk of GDM (appendix 2 table 1). P-values for decrease in BMI was not statistically significant (p>0.05).

No association was observed between a decrease in BMI and risk of c-section births (aOR 0.97 (95% CI 0.89-1.05), I^2=0.0%), whilst a moderate increase and substantial increase in BMI were associated with higher risks of c-section (aOR 1.16 (95% CI 1.06-1.26) I^2=53.5%) and aOR 1.72 (1.32-2.24) I^2=89.1%), respectively) (figure 4). Both moderate and substantial increase in BMI were statistically significant (p<0.05) (appendix 2 table 1).

A decrease in BMI (>1 BMI unit) was associated with an increase in SGA births (aOR 1.31 (95% CI 1.06-1.63, I^2=53.5%), whilst an increase in BMI was associated with a decreased risk of SGA births compared with the reference category (aOR 0.83 (95% CI 0.70-0.99), I^2=56.8% (figure 5). Both of these results are statistically significant (appendix 2 table 1).

Outcomes grouped by BMI before first pregnancy

Some studies divided women into women with a BMI of less than 25 at their first pregnancy (normal) and women with a BMI over 25 at their first pregnancy (overweight/obese).

Women of normal BMI (<25) at beginning of first pregnancy are at a higher risk of LGA babies if they have a substantial increase of BMI (OR 2.10 (95% CI 1.93-2.29), I^2=7.7%) compared with women who had an overweight/obese BMI (≥25) at the beginning of first pregnancy (OR 1.69 (95% CI 1.37-2.09), I^2=86.2%) (see appendix 2 table 2 for statistical significance). The same trend is apparent in a moderate increase of BMI (an increase of between 1 and 3 units) (appendix 3 fig 1 and 2).

Women of normal BMI (<25) at beginning of first pregnancy are at a higher risk of GDM if they have a substantial increase of BMI (OR 3.10 (95% CI 2.74-3.50), I^2=0.0%) compared with women who had an overweight/obese BMI (≥ 25) at the beginning of first pregnancy (OR 1.82 (95% CI 1.34-2.48), I^2=51.6%) (appendix 3 fig 3 and 4). The same trend is apparent in a moderate increase of BMI.

Women of normal BMI (<25) at beginning of first pregnancy are at a higher risk of c-section if they have a substantial increase of BMI (OR 1.70 (95% CI 1.34-2.16), I^2=87.7%) compared with women who had an overweight/obese BMI (≥ 25) at the beginning of first pregnancy (OR 1.52 (95% CI 0.84-2.75), I^2=78.0%) (appendix 3 fig 5 and 6). The same trend is apparent in a moderate increase of BMI. However, the confidence intervals of these two odds ratios overlap and therefore the statistical significance can be questioned.

One study[23] found that women of normal BMI (<25) who lose weight during the inter-pregnancy interval are at a similarly strong risk of SGA (aOR 1.76, 1.35-2.28) compared with women of an overweight/obese BMI (>25) who lose weight (aOR 1.73, 1.18-2.54).

Sensitivity analysis

Sensitivity analysis was assessed by removing studies that had a high level of bias (<3 on the Cochrane analysis of bias) or were of low quality according to the Newcastle-Ottawa scale (≤4 stars). Removal of low quality studies made limited difference to the results and the direction of effect remained the same. For LGA in women with a BMI < 25 results before removal of studies included decrease in BMI (aOR 0.65 (0.49-0.86), I^2=79.9%),

moderate increase in BMI (aOR 1.62 (1.54-1.71), I^2=0%) and substantial increase (aOR 2.10 (1.93-2.29), I^2=7.7%). After sensitivity analysis, heterogeneity for each of these groups decreased (appendix 4 table 1).

Heterogeneity

Generally, an I^2 value of 25% is considered low, 50% moderate and 75% high.[29] This value is thought to reflect the proportion of between-study variance not explained by sampling. When pooling results from population-based observational studies and the type of research used in this paper, it is impossible to control all possible confounders which is why a certain level of heterogeneity could be expected. As Higgins (2008) comments, if the predefined eligibility criteria and data are correct, any level of heterogeneity is acceptable, given that the authors can analyse the heterogeneous studies appropriately.[30] Analysis in this paper included random-effects analysis and sensitivity analysis. Further analysis of heterogeneity in this review is warranted; however, the Cochrane handbook recommends that meta-regression should not be completed if there are fewer than ten studies in a meta-analysis.[31] Further, it has been stated that this corresponds to ten studies for each covariate in meta-regression.[32] Due to this, the sources of heterogeneity will instead be discussed in limitations.

DISCUSSION

Major findings

This study found that an interpregnancy BMI decrease is associated with a reduced risk of LGA births (aOR 0.70 (95% CI 0.55-0.90) p<0,001), reduced risk of macrosomia (aOR 0.50 (95% CI 0.35-0.71) and GDM (aOR 0.80 (95% CI 0.62-1.03), and an increased risk of SGA (aOR 1.31 (95% CI 1.06-1.63, p=0.01) compared with reference category of women who retained BMI. A substantial increase in interpregnancy BMI (> 3 BMI units) is associated with an increased risk of LGA (aOR 1.85 (95% CI 1.71-2.00) p<0.001), GDM (aOR 2.28 (95% CI 1.97-2.63) p<0.001), c-section (aOR 1.72 (95% CI 1.32-2.24) p<0.001) and macrosomia (aOR 1.54 (95% CI 0.94-2.50) compared with the reference category (no weight change). An increase in BMI is associated with a decreased risk of SGA (aOR 0.83 (95% CI 0.70-0.99, p=0.044) Results did not change after sensitivity analyses removing low quality and studies with high bias. We believe this is the first systematic review and meta-analysis completed on the topic of interpregnancy weight change and adverse pregnancy outcomes in women from parity 0 to 1. When results are further analysed according to prepregnancy BMI (<25 or over 25 kg/m^2), women with a normal prepregnancy BMI at first pregnancy are at higher risk of LGA (aOR 2.10 (95% CI 1.93-2.29)) and GDM (aOR 3.10 (95% CI 2.74-3.50)) compared with women with a BMI ≥25.

Interpretation of major findings

It is known that obesity is the most common risk factor for insulin insensitivity.[33] A possible biological relation between obesity and adverse perinatal outcomes is the role of glucose and insulin insensitivity in pregnancy. The Pedersen Hypothesis, first suggested in 1952, stipulates that a higher-than-normal level of glucose (the main energy substrate of the foetus) transferred via the placenta to the foetus stimulates the release of insulin and insulin-like growth factors in the foetus, causing large for gestational age infants or macrosomic births.[34] This has been supported by research showing that high postprandial glucose concentration predicts large birth weight and hypoglycaemia is associated with growth restriction.[35]

An overweight or obese pregnant woman has a 50-60% increase in insulin insensitivity compared with a normal weighted pregnant woman.[36] Associated hyperglycaemia for the infant, as well as an increase in the release of free fatty acids and triglycerides from adipose stores have been studied to be associated with increased birth weight and adiposity of the offspring.[37] The reduction in insulin sensitivity as a result of interpregnancy weight gain may lead to higher levels of GDM, LGA, macrosomia and subsequent caesarean sections. On the contrary, weight loss and its association with increased insulin sensitivity may therefore result in reduced numbers of GDM and increased number small for gestational age births. This may be as increased insulin sensitivity may cause less glucose to cross the placenta and thus there is an increased risk of SGA. Studies researching inter-pregnancy weight change in women over three consecutive pregnancies supports this finding, with weight loss associated with an increased risk of low placental weight and SGA births.[38] Studies have found that not all interpregnancy weight gain is attributed to weight gain in pregnancy: 0.45 kg can be credited to the trend of weight gain over time.[39] Research has also shown that women with a BMI ≥25 before pregnancy experience greater increases in postpartum body weight, and weight change 12 months postpartum is largely influenced by the prepregnancy body weight.[40] Interpregnancy weight gain as a result of both insufficient gestational weight loss after the previous pregnancy, combined with the normal trend of weight gain over time may have an additive or synergistic effect and result in further lowering of insulin sensitivity.

Strengths

We believe this is the first systematic review and meta-analysis completed on the topic of interpregnancy weight change and adverse pregnancy outcomes in women from parity 0 to 1 with singleton births. This review synthesised the available evidence on the association of interpregnancy weight change, defined as the difference in BMI in early pregnancy between successive pregnancies, on major complications. The findings of eleven cohort studies showed that interpregnancy weight gain was strongly associated with an increased risk of namely, GDM, CS, and large birth weight babies among all women regardless of initial BMI status, and a decrease in risk of SGA. Conversely, interpregnancy weight loss was strongly associated with a reduced risk of GDM, and large birth weight in the second-born offspring, an increase in risk of SGA, but no detectable association with the rate of CS. The criteria outlined in the PRISMA statement and the Cochrane Handbook for Systematic Reviews of Intervention was adhered to, and this can be seen in table 2 appendix 4. Furthermore, the MOOSE checklist of recommendations for reporting meta-analyses of observational studies was followed. Results did not change even after sensitivity analyses of high methodological quality studies.

Studies included in this review were cohort studies with generally large sample sizes, resulting in a large pooled sample of almost one million women. The strengths of using these studies meant that they are population-based, with a generally representative population. Outcomes were classified in the same way in each study and for most of the outcomes it is objectively defined to classify if the outcome occurred or not, reducing a possible bias of assessment of outcome. In addition to this, the reliability of medical records has shown good level of both inter-rater and intra-rater reliability.[41] This review used two different ways of analysing the quality of studies and possible sources of bias – the Newcastle-Ottawa scale and the Cochrane analysis of bias. All studies had at least four stars on the NOS, and sensitivity analysis was performed to remove low quality studies or studies with a high bias. All studies used adjusted odds ratios to adjust for confounding factors such as age, race, interpregnancy interval and previous adverse outcome in first pregnancy.

Parity and previous diabetes mellitus were adjusted for in this review, which included only primiparous women (from parity 0 to 1) with no previous history of type II diabetes mellitus (T2DM). Compared with low multiparity, primigravid women have different risks and complications whilst higher parity (parity 4 upwards) has been associated with increased obstetric complications and neonatal morbidity.[42] Furthermore, T2DM during pregnancy is associated with higher risks of stillbirth, perinatal mortality and congenital malformations.[43] Excluding these factors and taking into account that all papers included in this review were adjusted for multiple confounding variables means that it is less likely that the results are due to confounding or systematic bias and more likely to reflect genuine causality. Further, this review aimed to minimise heterogeneity in several ways: each study was assessed according to if confounding factors were appropriately recognised and adjusted for, weight change was stratified into three categories in order to effectively combine results that could be compared, and sensitivity analysis was carried out by removing low quality studies with a high level of bias.

Limitations

Originally in the search strategy and PROSPERO registration other outcomes were aimed to be included (preterm birth, pre-eclampsia, perinatal death), however there was a lack of relevant data and low-quality studies linked to these outcomes and thus these outcomes were excluded from this report. Other deviations from the protocol included the population definition being expanded to all women and not just overweight/obese women which enhances the external validity of the study. Subgroup analyses was not included in the registration as we did not have details of the analyses at the time of registration and this addition provide further nuance on our findings. Despite attempts to limit heterogeneity as described above, the high heterogeneity means that it may be misleading to combine results to provide an average estimate of exposure, especially in light of the relatively small sample sizes in each outcome. Conclusions should therefore be interpreted with caution and considered largely hypothesis-generating. The effect of confounders could not be assessed by comparing unadjusted and adjusted odds ratios, as unadjusted data was not available nor was it possible to calculate based on the available data. A random-effects model was used rather than a fixed effect model to assess heterogeneity in the meta-analysis as it considers in-between study variation. Further statistical analysis to assess heterogeneity such as meta-regression was not performed due to the limited number of studies for each outcome - however, possible sources of heterogeneity are listed in table 4. Many of the studies report missing data and have categorised BMI change differently (for example units, WHO groups or percentages), making it difficult to combine data in a meaningful and objective way. However, this was addressed with subgroup analysis and by stratifying weight change into categories. The use of observational cohort studies means that it is very difficult to adjust for all possible confounding factors, leading to an inevitable heterogeneity between studies. Publication bias could not be assessed due to the small amount of studies in each primary outcome, with most of the outcomes having between 2-5 studies in each category. It has been suggested that less than 10 studies is not adequate in order to complete a funnel plot and would thus be underpowered.[44]

Table 4: Possible reasons to explain high heterogeneity (I^2) found in the review

Possible sources of heterogeneity	Example
Classification of BMI change	Units (kg/m^2), WHO groups (underweight, obese)
Different population design	Sources of data varied, locations of studies varied
Differences in study design	Use of self-report for height and weight
Missing data	Missing data in original studies could not be controlled for
Small number of studies for each outcome	Between 2 to 4 studies for each outcome
Unknown factors (residual confounding variables)	Breastfeeding, family history, diet, exercise

BMI is closely linked to lifestyle factors, diseases, and genetic traits that are correlated with the outcome of pregnancy. Although studies adjusted for multiple confounding factors, there are additional confounders that could affect results that were not adjusted for, including breastfeeding, diet, exercise and genetics. In addition, the effect of obesity may be confounded by several comorbidities that are possibly undiagnosed. Breastfeeding may be a possible confounding factor in interpregnancy weight change as women who breastfeed have less weight post-partum, which is thought to be due to the high calorie usage during breastfeeding, however this is contentious.[45] The lack of information regarding diet and exercise means that the reduced risk of adverse outcomes in pregnancy may not be due to the weight loss but to other aspects that are changed in a healthier lifestyle. Furthermore, interpregnancy interval and gestational weight gain were adjusted for in some studies but the effect of these should not be underestimated. The shorter the interpregnancy interval, the higher the risk of LGA.[46] The shorter the time between pregnancies or the more gestational weight gain, the more difficult it may be for women to lose the weight gained from the previous pregnancy. All future studies should adjust for interpregnancy interval. Gestational weight gain is responsible for interpregnancy weight gain after the first pregnancy, but is a potential mediator in the second pregnancy and therefore it is questionable whether it should be adjusted for.

This review focused on singleton births from parity 0 to 1, with all of the studies coming from high-income Western countries. This limits the generalisability of the conclusions to lower income countries. Even though this review did exclude women with previous type 2 diabetes mellitus, it should be noted that due to the lack of a universal screening for GDM, some women with GDM may have been missed. This is difficult to assess and control, and due to the controversy surrounding screening for GDM and the lack of good quality evidence-based data, it has been unable to be determined whether or not screening would have an important effect on adverse pregnancy outcomes.[47]

Future Research

This review highlights that observational studies can help give direction for future research. To help clarify the association between interpregnancy weight change and adverse pregnancy outcomes, a precise way of measuring BMI change needs to be implemented and subgroup definitions should be consistent. Due to the problems with low rate of outcome, large studies free of bias associated with recall and self-report need to be undertaken that adhere to STROBE guidelines and ICHOM standards. Future researchers should also consider the possible synergistic and additive effect of normal weight gain over time combined with insufficient postpartum weight loss and how it can affect pregnancy outcomes.

Large-scale studies on specific classes of obesity should be conducted to study the rate of weight change and if it affects the magnitude of association. The National Institute for Health Research submitted a call for research regarding weight management after pregnancy, stating that excessive gestational weight gain or postpartum weight retention may be cumulative over successive pregnancies.[48] The SWAN feasibility study (Supporting Women with Postnatal Management) is aiming to study women allocated to an intervention (weight management group) or control group at 36 weeks of pregnancy and followed up 12 months postnatally. This will be one of the first studies to look at postnatal intervention in weight control in the UK.[49] Furthermore, Slimming World undertook a study in Cardiff called HELP (Health Eating and Lifestyle in Pregnancy) to look at the benefits of behaviour changes and weight management during pregnancy in the UK. The study was underpowered but healthy eating and lifestyle intervention was acceptable to help women control their weight

change during pregnancy and postpartum.[50] Other feasibility studies such as PRAM (Pregnancy and Weight Monitoring) are currently underway and evaluation of the efficacy of these interventions is expected in the future.[51]

Implications for policy makers and clinicians

NICE postnatal guidelines currently suggest that women with a BMI > 30 kg/m^2 at the 6-8 week postnatal check are referred for advice regarding weight loss. This review provides some evidence to suggest that postnatal weight interventions are needed, as even moderate changes in interpregnancy BMI can lead to increased risks of adverse pregnancy outcomes for the mother and baby. However, the effect of weight loss on increased risk of SGA should not be forgotten.

The Institute of Medicine has introduced optimal weight gain for BMI-specific ranges in pregnancy, though NICE has recommended that these guidelines should be researched to see if they are appropriate for the UK population.[52] Based on the results of this review, it can be suggested that clinicians should be aware of the risk in women whose BMI has changed after their first pregnancy. Particularly women who wish to conceive again shortly after birth of their first child should be monitored after pregnancy to attempt to keep BMI change to a minimum. Importantly, women who are at a healthy weight are not without risk. Therefore, not only is monitoring gestational weight change important in preventing adverse outcomes in pregnancy, but interpregnancy weight change can also influence maternal and foetal outcomes.

CONCLUSION

This study is the first systematic review and meta-analysis to assess the association of interpregnancy weight change on five adverse pregnancy outcomes. The results show that interpregnancy weight gain increases the risk of GDM, CS and LGA, but lowers the risk of SGA, while weight reduction lowers the risk of GDM and LGA and increases the risk of SGA. In particular, it is noted that weight gain from normal weight is more detrimental than from a higher weight in regard to GDM, LGA and C-section. Keeping weight stable between consecutive conceptions is important in order to lower risk of adverse pregnancy outcomes. However, further research is needed to substantiate the evidence presented in this review.

Figure Legends:

Figure 1: 2009 PRISMA flow diagram showing results of literature search

Figure 2: Forest plot showing change in interpregnancy weight and the risk of large for gestational age births in all women relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

Figure 3: Figure 5: Forest plot showing change in interpregnancy weight and the risk of gestational diabetes mellitus in all women relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

Figure 4: Figure 5: Forest plot showing change in interpregnancy weight and the risk of Caesarean section in all women relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

Figure 5: Forest plot showing change in interpregnancy weight and the risk of small for gestational age births in all women relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

FOOTNOTES

Acknowledgements: We would like to thank all reviewers for their helpful comments.

Contributors: EO formulated the research question and wrote and reviewed the report. SM did the literature search, extracted and selected articles, completed the meta-analysis, and wrote the report. OS did the literature

search, extracted and selected articles, and contributed to writing the paper. PS completed the meta-analysis. DB and LP contributed to the writing of the paper.

Funding: EO is partly funded by the Big Lottery Fund, NIHR, Tommy's Charity and Guy's and St Thomas' Charity. LP is partly funded by Tommy's Charity. PS is partly funded by CLAHRC South London (NIHR) and Tommy's Charity.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: None required

Data sharing: No additional data available

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

REFERENCES

1. Yu Z, Han S, Zhu J, Sun X, Ji C. Pre-Pregnancy Body Mass Index in Relation to Infant Birth Weight and Offspring Overweight/Obesity: A Systematic Review and Meta-Analysis. PLoS ONE 2013; 8: e61627.
2. Chu SY, Kim SY, Lau J, Schmid CH, Dietz PM, Callaghan WM, Curtis KM. Maternal obesity and risk of stillbirth: a metaanalysis. Am J Obstet Gynecol. 2007; 197: 223–8.
3. Jovanovič L, Liang Y, Weng W, Hamilton M, Chen L, Wintfeld N. Trends in the incidence of diabetes, its clinical sequelae, and associated costs in pregnancy. Diabetes/Metabolism Research and Reviews. 2015; 31: 707–716.
4. Balen AH, Anderson RA, Policy & Practice Committee of the BFS. Impact of Obesity on female reproductive health: British Fertility Society, Policy and Practice Guidelines. Hum Fertil (Camb). 2007; 10: 195–206.
5. Leddy MA, Power ML, Schulkin J. The Impact of Maternal Obesity on Maternal and Fetal Health. Reviews in Obstetrics and Gynecology. 2008; 1: 170–178.
6. Oteng-Ntim E, Varma R, Croker H, Poston L, Doyle P. Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis. BMC Medicine 2012; 10: 47.
7. Centers for Disease Control and Prevention. Recommendations to improve preconception health and health care - United States: a report of the CDC/ ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. MMWR 2006; 55: 1–22.
8. Whitworth M, Dowswell T. Routine pre-pregnancy health promotion for improving pregnancy outcomes. Cochrane Database of Systematic Reviews 2009; 4: CD007536.
9. Tieu J, Bain E, Middleton P, Crowther CA. Interconception care for women with a history of gestational diabetes for improving maternal and infant outcomes. Cochrane Database of Systematic Reviews 2013; 6: CD010211.
10. PROSPERO, International prospective register of systematic reviews. [Internet]. York: Centre for Reviews and Dissemination [cited 22 June 2016]. Available from: http://www.crd.york.ac.uk/PROSPERO
11. Cnattingius S, Villamor E. Weight change between successive pregnancies and risks of stillbirth and infant mortality: a nationwide cohort study. Lancet 2016; 387: 558–65.
12. Najafian M, Cheraghi M. Occurrence of Fetal Macrosomia Rate and Its Maternal and Neonatal Complications: A 5-Year Cohort Study. Obstet Gynecol 2012:e353791.
13. Centre for Maternal and Child Enquiries (CMACE) Maternal obesity in the UK: findings from a national project. (2010) London: CMACE.

14. American Diabetes Association. Gestational Diabetes Mellitus. Diabetes Care. 2004;27:88-90.
15. World Health Organisation body mass index (BMI) classification. (Website) Available on: www.who.int/bmi/index.jsp?introPage=intro_3.html. Last accessed 04 Feb 2017.
16. Bogaerts A, Van den Bergh BR, Ameye L, Witters I, Martens E, Timmerman D, Devlieger R. Interpregnancy weight change and risk for adverse perinatal outcome. Obstet Gynaecol 2013;122:999–1009.
17. Cheng C, Bommarito K, Noguchi A, Holcomb W, Leet T. Body mass index change between pregnancies and small for gestational age births. Obstet Gynecol 2004;104(2):286-292.
18. Ehrlich SF, Hedderson MM, Feng J, Davenport ER, Gunderson EP, Ferarra A. Changes in prepregnancy body mass indexes between pregnancies and the risk of gestational diabetes in a second pregnancy. Obstet Gynaecol. 2011;117: 1323–1330.
19. Getahun D, Ananth CV, Peltier MR, Salihu HM, Scorza WE. Changes in prepregnancy body mass index between the first and second pregnancies and risk of large-for-gestational-age birth. Am J Obstet Gynecol 2007;196:e1–e8.
20. Getahun D, Ananth CV, Oyelese Y, Chavez MR, Kirby RS, Smulian JC. Primary preeclampsia in the second pregnancy: effects of changes in prepregnancy body mass index between pregnancies. Obstet Gynecol 2007;110:1319–1325.
21. Jain AP, Gavard JA, Rice JJ, Catanzaro RB, Artal R, Hopkins SA. The impact of interpregnancy weight change on birthweight in obese women. Am J Obstet Gynecol. 2013;208:e1–e7.
22. Whiteman VE, McIntosh C, Rao K, Mbah AK, Salihu HM. Interpregnancy BMI change and risk of primary caesarean delivery. J Obstet Gynaecol 2011;31:589–593.
23. Whiteman VE, Aliyu MH, August EM, McIntosh C, Duan J, Alio AP, Salihu HM. Change in body mass index between pregnancies and risk of gestational and type two diabetes. Arch Obstet Gynaecol 2011;284:235–240.
24. Wallace JM, Bhattacharya S, Campbell DM, Horgan GW. Inter-pregnancy weight change impacts placental weight and is associated with the risk of adverse pregnancy outcomes in the second pregnancy. BMC Pregnancy Childbirth 2014;14: 40.
25. Wallace JM, Bhattacharya S, Campbell DM, Horgan GW. Inter-pregnancy Weight Change and risk of recurrent pregnancy complications. PLoS One 2016;11:e0154812.
26. Villamor E, Cnattingius S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. Lancet 2006;368:1164–1170.
27. Wells G, Shea B, O'Connell J & Roberson J. 2011 The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. (Website) Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp Last accessed: 28 Feb 2017
28. Higgins JPT, Altman DG, Gotzshe PC, Juni P, Moher D, Oxman AD. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;3443:d5928.
29. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.
30. Higgins JPT. Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. Int J Epidemiol 2008;37:1158-1160.
31. Higgins JPT, Altman DG, Sterne JAC (2011). Chapter 9: Meta-regression In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 ed. Higgins JPT & Green S. [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org. Last accessed: 14 Mar 2017.
32. Borenstein ML, Hedges V, Higgins JPT, Rothstein HR. (2009) Chapter 20: Meta-regression. In: Introduction to meta-analysis. Chichester: John Wiley & Sons Ltd.
33. Catalano PM. Obesity, Insulin Resistance and Pregnancy Outcome. Reproduction 2010;140:365–371.
34. Pedersen J (1952) Diabetes and pregnancy: blood sugar of newborn infants [PhD thesis], Danish Science Press, Copenhagen (Denmark)

35. Scholl TO, Sowers M, Chen X, Lenders C. Maternal Glucose Concentration Influences Fetal Growth, Gestation, and Pregnancy Complications. Am J Epidemiol 2001;154:514-520.

36. Catalano PM, Hanguel-De Mouzon S. Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic? AJOG 2011;204:479-487.

37. Di Cianni G, Miccoli R, Volpe L. Maternal triglyceride levels and newborn weight in pregnant women with normal glucose tolerance. Diabet Med 2005;22: 21–25.

38. Wallace JM, Bhattacharya S & Horgan GW. Weight change across the start of three consecutive pregnancies and the risk of maternal morbidity and SGA birth at the second and third pregnancy. PloS ONE 2017;12(6):e0179589.

39. Greene GW, Smiciklas-Wright H, Scholl TO, Karp RJ. Postpartum Weight Change: How Much of Weight Gained in Pregnancy Will Be Lost At Delivery? Obstet Gynecol 1988;71:701-707.

40. McKeown T, Record RG. The influence of weight and height on weight changes associated with pregnancy in Women. J Endocrinol 1957;15:423-429

41. Ock M, Lee S, Jo MW, Lee JY, Kim SH. Assessing Reliability of Medical Record Reviews for the Detection of Hospital Adverse Events. J Prev Med Public Health 2015;48:239–248.

42. Bai J, Wong FWS, Bauman A, Mohsin M. Parity and pregnancy outcomes. AJOG 2002;186:274-278.

43. Ray JG, Vermeulen MJ, Shapiro JL, Kenshole AB. Maternal and neonatal outcomes in pregestational and gestational diabetes mellitus, and the influence of maternal obesity and weight gain: the DEPOSIT study. QJM: An international Journal of Medicine 2001; 94 (7): 347-356.

44. Lau J, Ionnidis J, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. BMJ;2006:333(7568):597-600.

45. Allen J, Hector D. Benefits of breastfeeding. N S W Public Health Bull 2005;16:42-46.

46. Zhu BP. Effect of interpregnancy interval on birth outcomes: findings from three recent US studies. Int J Gynaecol Obstet 2005;89:S25-S33.

47. Brody SC, Harris R, Lohr K. Screening for gestational diabetes: a summary of the evidence for the U.S. Preventive Services Task Force. Obstet Gynecol 2003;101:380-392.

48. National Institute of Health Research (2014) 14/67 Weight management after pregnancy. Available on: njl-admin.nihr.ac.uk/document/download/2007433 Last accessed: 14 Mar 2017

49. IRAS. Supporting Women with Postnatal Weight MAnagemeNt – SWAN Feasibility Trial Protocol. (2016) Available on: njl-admin.nihr.ac.uk/document/download/2007612 Last accessed: 14 Mar 2017

50. Jewell K, Avery A, Barber J, Simpson S. The healthy eating and lifestyle in pregnancy (HELP) feasibility study. BMJ 2014;22:727-736.

51. Sanders J (2016) PRAM. Available on: cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/pram Last accessed: 14 Mar 2017.

52. National Institute for Health and Care Excellence (2010) Weight management before, during and after pregnancy: Public health guideline. Available on: nice.org.uk/guidance/ph27 Last accessed: 14 Mar 2017

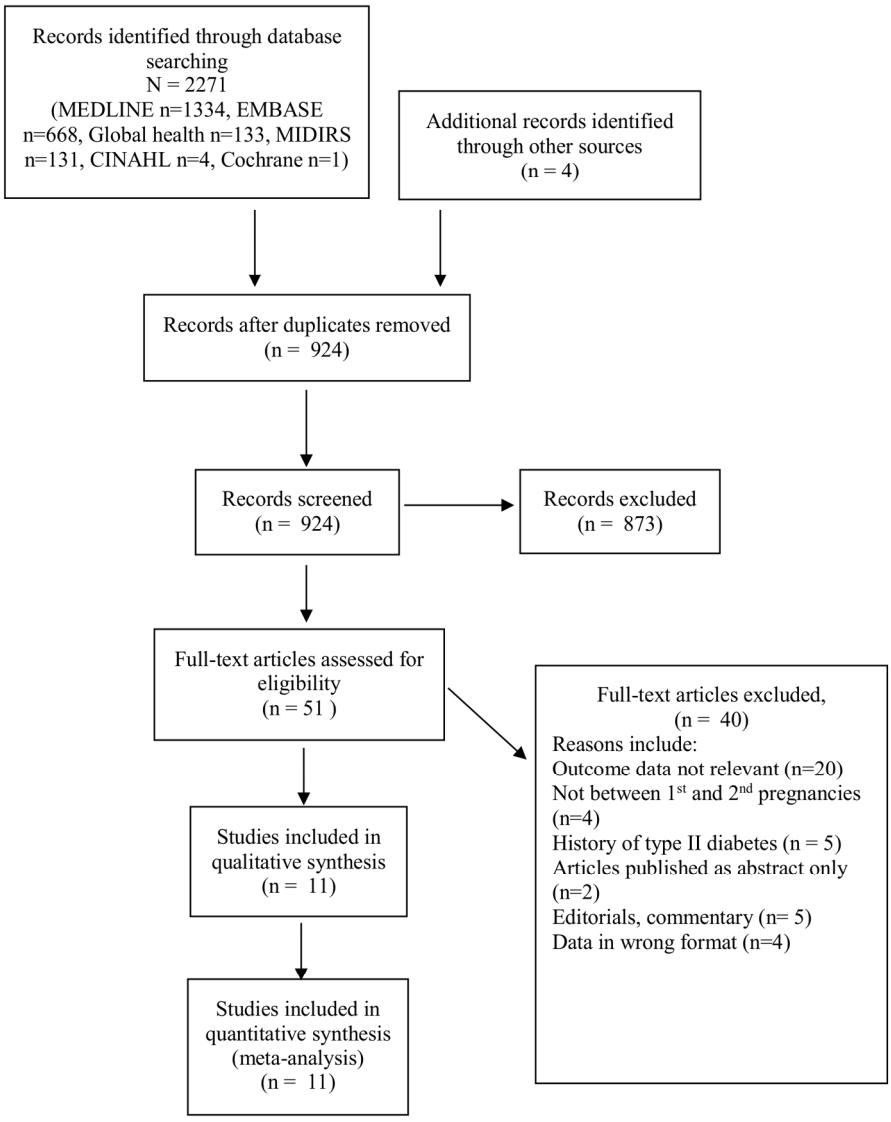

Figure 1: 2009 PRISMA flow diagram showing results of literature search

164x196mm (300 x 300 DPI)

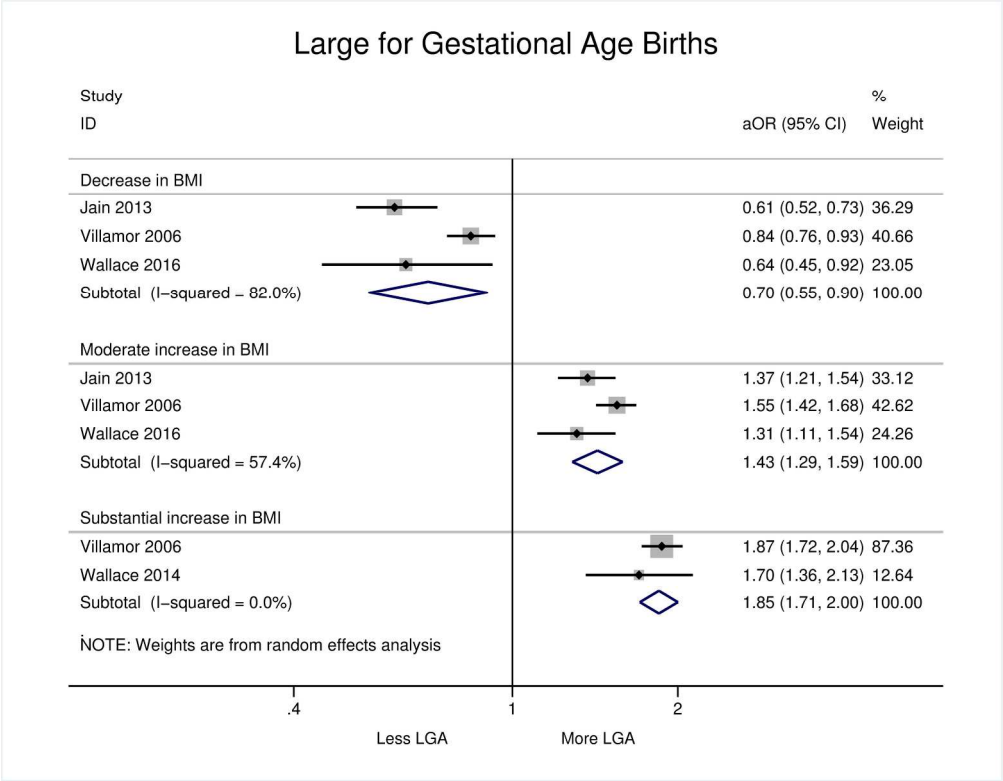

Figure 2: Forest plot showing change in interpregnancy weight and the risk of large for gestational age births in all women relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

216x168mm (300 x 300 DPI)

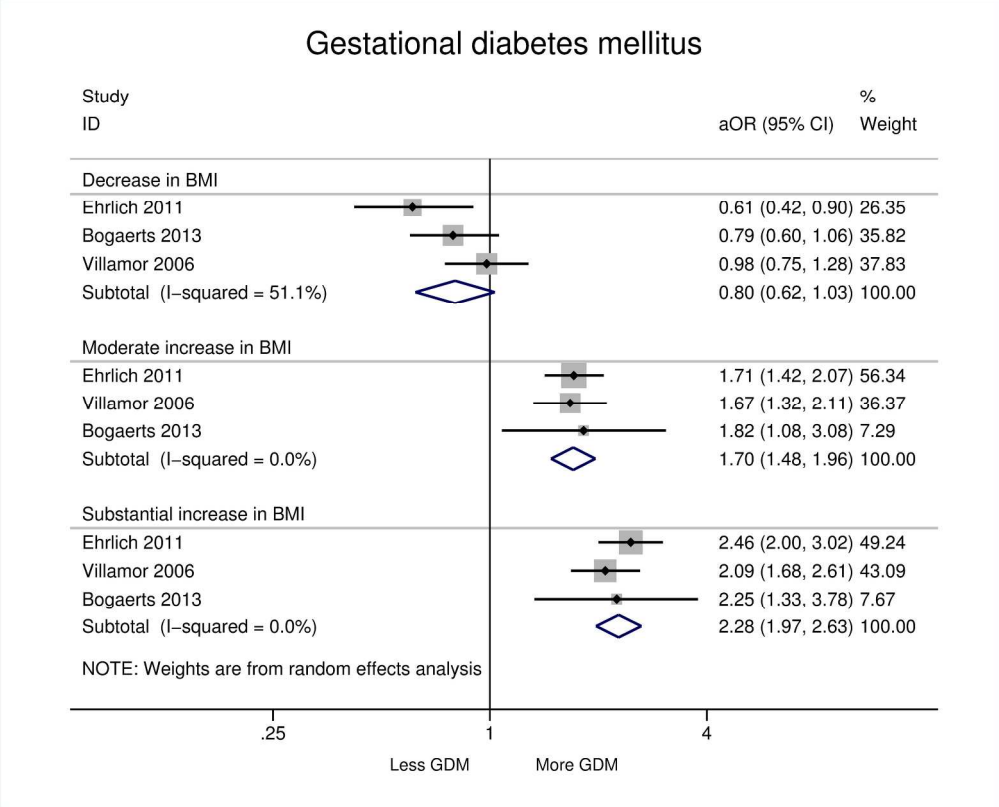

Figure 3: Figure 5: Forest plot showing change in interpregnancy weight and the risk of gestational diabetes mellitus in all women relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

226x183mm (300 x 300 DPI)

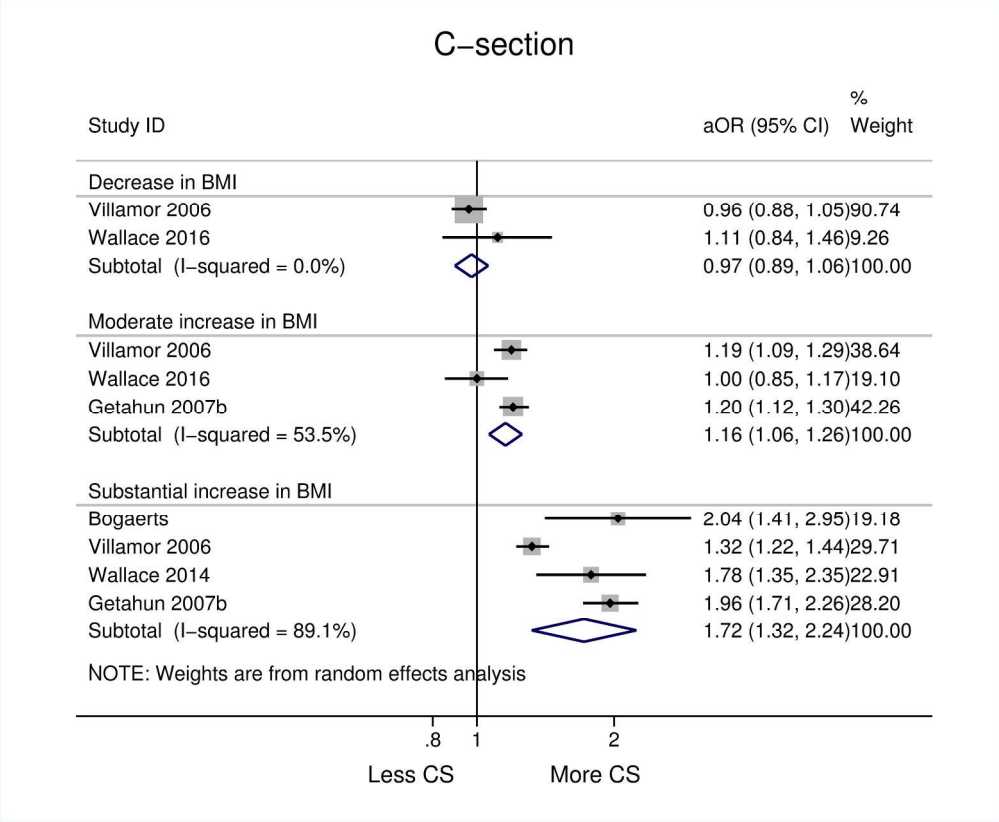

Figure 4: Figure 5: Forest plot showing change in interpregnancy weight and the risk of Caesarean section in all women relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

230x190mm (300 x 300 DPI)

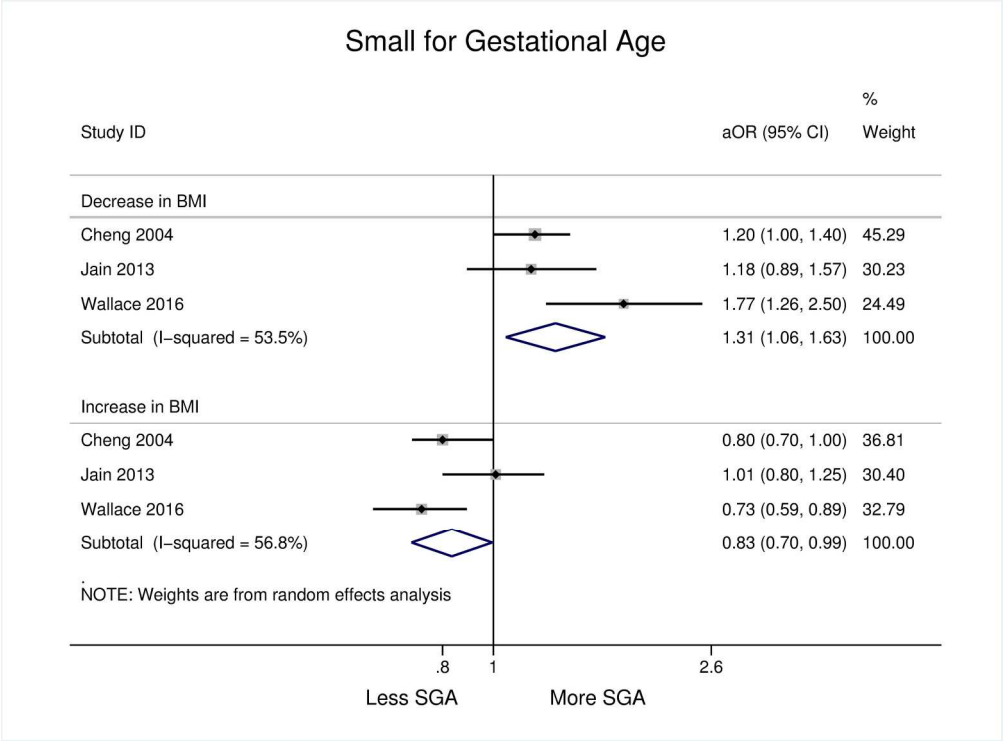

Figure 5: Forest plot showing change in interpregnancy weight and the risk of small for gestational age births in all women relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

203x150mm (300 x 300 DPI)

APPENDIX 1

Table 1: **Criteria for the Newcastle-Ottawa Scale regarding star allocation to assess quality of studies (out of a total of seven stars)**

Criteria	Acceptable (star awarded):	Unacceptable (star not awarded):
Representativeness of exposed cohort	Population-based	Hospital-based
Selection of non-exposed cohort	Same setting as exposed cohort	Different setting from exposed cohort
Ascertainment of exposure	Secure records or directly measured	Self-reported information
Comparability	Excluded or adjusted for prior outcome in analysis	No exclusion of prior outcome in previous pregnancy
	Adjusted for age, race, smoking and interpregnancy interval	Did not adjust for age, race, smoking and interpregnancy interval
Outcome of interest	Secure records or directly measured	Self-reported information
Adequacy of follow-up	Adjusted for missing data or follow-up > 1 month.	No statement regarding missing data. No follow-up after birth.

Table 2: Quality assessment of studies using a modified Newcastle-Ottawa scale for assessing studies in the systematic review of interpregnancy weight change and pregnancy outcome

Study ID	Selection			Comparability*	Outcome		Total (7⋆)
	Representativeness of exposed cohort (⋆)	Selection of non-exposed cohort (⋆)	Ascertainment of exposure (⋆)	(⋆⋆)	Assessment of outcome (⋆)	Adequacy of follow up (⋆)	
Bogaerts 2013	⋆	⋆	-	⋆⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Cheng 2004	⋆	⋆	-	⋆⋆	⋆	⋆	⋆⋆⋆⋆⋆⋆ (6)
Ehrlich 2011	-	⋆	⋆	⋆⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Getahun 2007a	⋆	⋆	-	⋆ -	⋆	-	⋆⋆⋆⋆ (4)
Getahun 2007b	⋆	⋆	-	⋆⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Jain 2013	⋆	⋆	-	⋆⋆	⋆	⋆	⋆⋆⋆⋆⋆⋆ (6)
Villamor 2006	⋆	⋆	⋆	⋆⋆	⋆	-	⋆⋆⋆⋆⋆⋆ (6)
Wallace 2014	-	⋆	⋆	⋆⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Wallace 2016	⋆	⋆	⋆	- ⋆	⋆	-	⋆⋆⋆⋆⋆ (5)
Whiteman 2011a	⋆	⋆	-	⋆⋆	⋆	⋆	⋆⋆⋆⋆⋆⋆ (6)
Whiteman 2011b	⋆	⋆	-	⋆⋆	⋆	⋆	⋆⋆⋆⋆⋆⋆ (6)

***** Comparability assessed as the following: one star rewarded if study excluded or adjusted for outcome in first pregnancy, another star rewarded if study adjusted for age, race, smoking and interpregnancy interval

Table 3: Risk of bias assessment (modified from Cochrane Tool to Assess Risk of Bias in Cohort Studies and EPOC Data Collection Form)[29]

Study ID	Allocation concealment (selection bias)	Assessment of exposure (self-report)	Outcome of interest present at beginning	Incomplete data	Selective reporting (reporting bias)	Total score*
Bogaerts 2013	+	-	+	+	-	3
Cheng 2004	+	-	+	+	+	4
Ehrlich 2011	-	+	+	?	+	3
Getahun 2007a	+	-	?	?	+	2
Getahun 2007b	+	-	+	?	+	3
Jain 2013	+	-	+	+	+	4
Villamor 2006	+	+	+	?	+	4
Wallace 2014	-	+	+	?	+	3
Wallace 2016	+	+	-	?	+	3
Whiteman 2011a	+	-	+	+	+	4
Whiteman 2011b	+	-	+	+	+	4

*Total score: points awarded based on number of "+" or low risk of bias
+ = Low risk of bias, ? = Unclear risk of bias, - = High risk of bias

APPENDIX 2

Table 1: Overall statistical significance of effect size = 1

Outcome	Change in BMI	Z value	P-value
LGA	Decrease	z= 2.77	p = 0.006
	Moderate increase	z= 6.63	p = 0.000
	Substantial increase	z= 15.09	p = 0.000
GDM	Decrease	z= 1.72	p = 0.085
	Moderate increase	z= 7.38	p = 0.000
	Substantial increase	z= 11.16	p = 0.000
C-section	Decrease	z= 0.64	p = 0.524
	Moderate increase	z= 3.39	p = 0.001
	Substantial increase	z= 4.01	p = 0.000
SGA	Decrease	z= 2.45	p = 0.014
	Increase	z= 2.02	p = 0.044

Table 2: Overall statistical significant of effect size = 1 in subgroups of women with a BMI before pregnancy of < 25 or ≥ 25

Outcome	Change in BMI	Z value	P-value
LGA BMI < 25	Decrease	z= 2.99	p = 0.003
	Moderate increase	z= 17.90	p = 0.000
	Substantial increase	z= 17.07	p = 0.000
LGA BMI ≥ 25	Decrease	z= 2.09	p = 0.036
	Moderate increase	z= 1.14	p = 0.144
	Substantial increase	z= 4.87	p = 0.000
GDM BMI < 25	Decrease	z= 2.11	p = 0.035
	Moderate increase	z= 4.03	p = 0.000
	Substantial increase	z= 3.83	p = 0.000
GDM BMI ≥ 25	Decrease	z= 2.42	p = 0.016
	Moderate increase	z= 13.75	p = 0.000
	Substantial increase	z= 18.11	p = 0.000
C-section BMI < 25	Decrease	z= 0.82	p = 0.415
	Moderate increase	z= 5.06	p = 0.000
	Substantial increase	z= 4.33	p = 0.000
C-section BMI ≥ 25	Decrease	z= 3.05	p = 0.002
	Moderate increase	z= 2.10	p = 0.036
	Substantial increase	z= 1.37	p = 0.170

APPENDIX 3

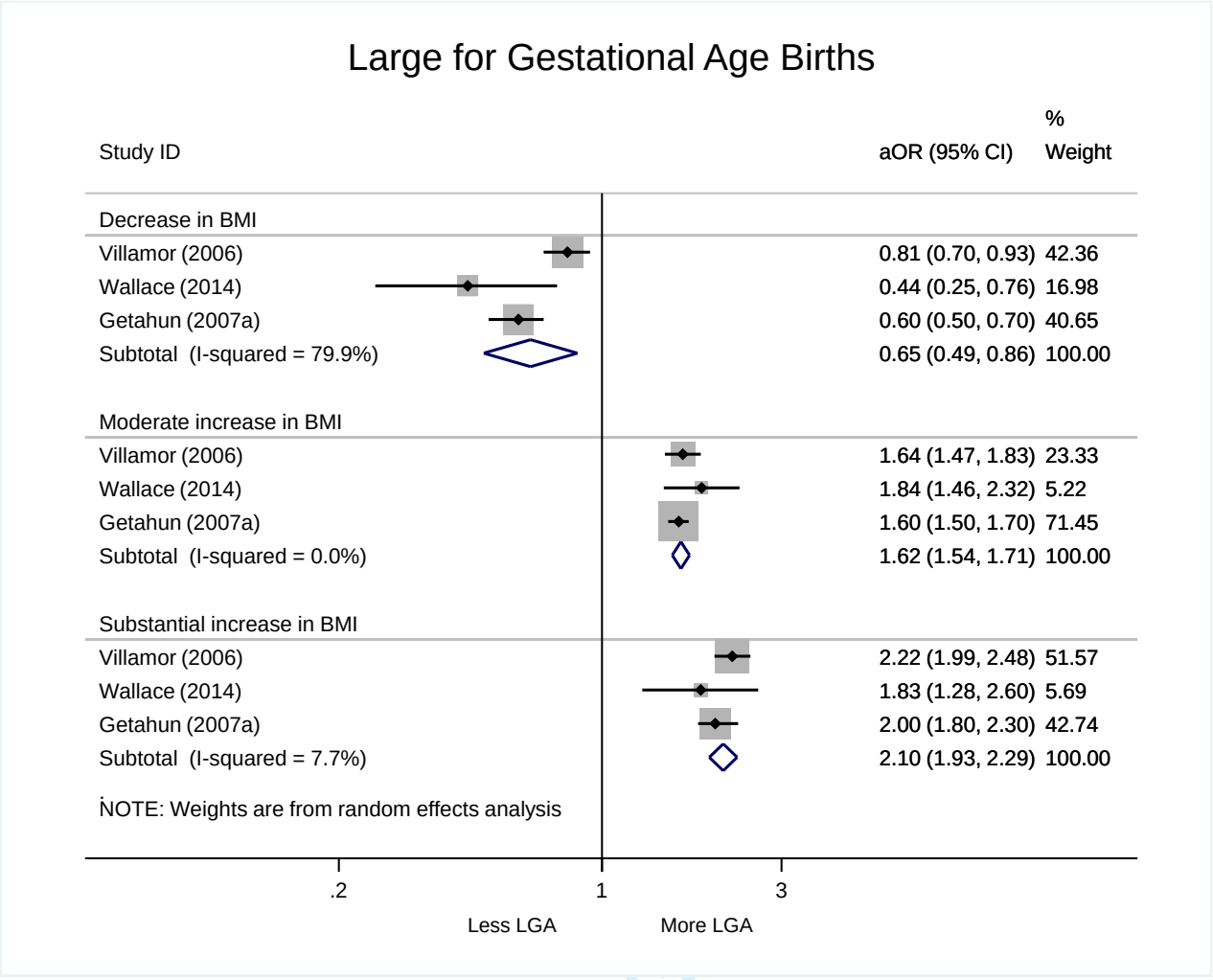

Figure 1: Forest plot showing change in interpregnancy weight and the risk of large for gestational age births in the subsequent pregnancy for women with normal BMI (< 25) at the beginning of first pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

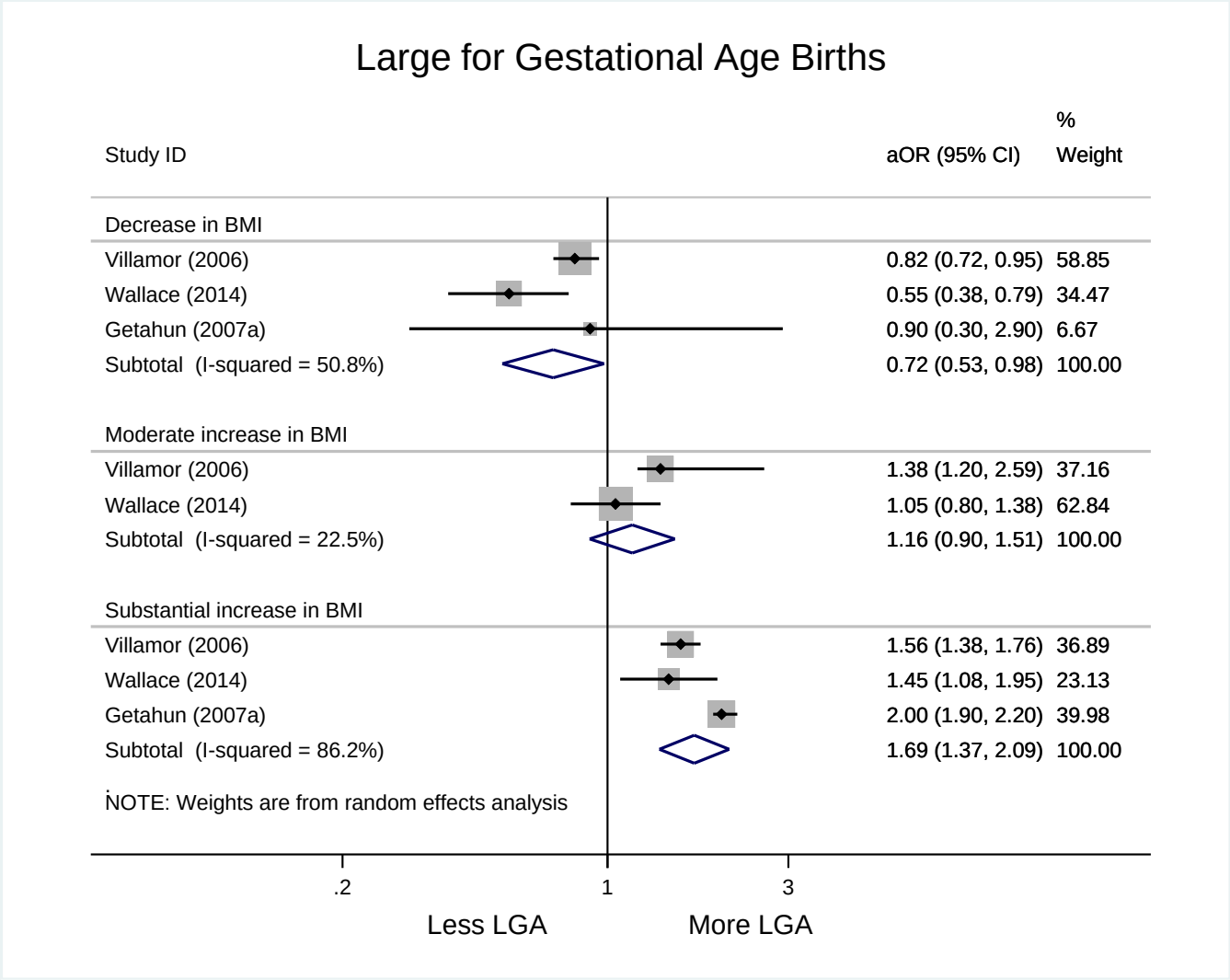

Figure 2: Forest plot showing change in interpregnancy weight and the risk of large for gestational age births in the subsequent pregnancy for women with overweight/obese BMI (≥ 25) at the beginning of first pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

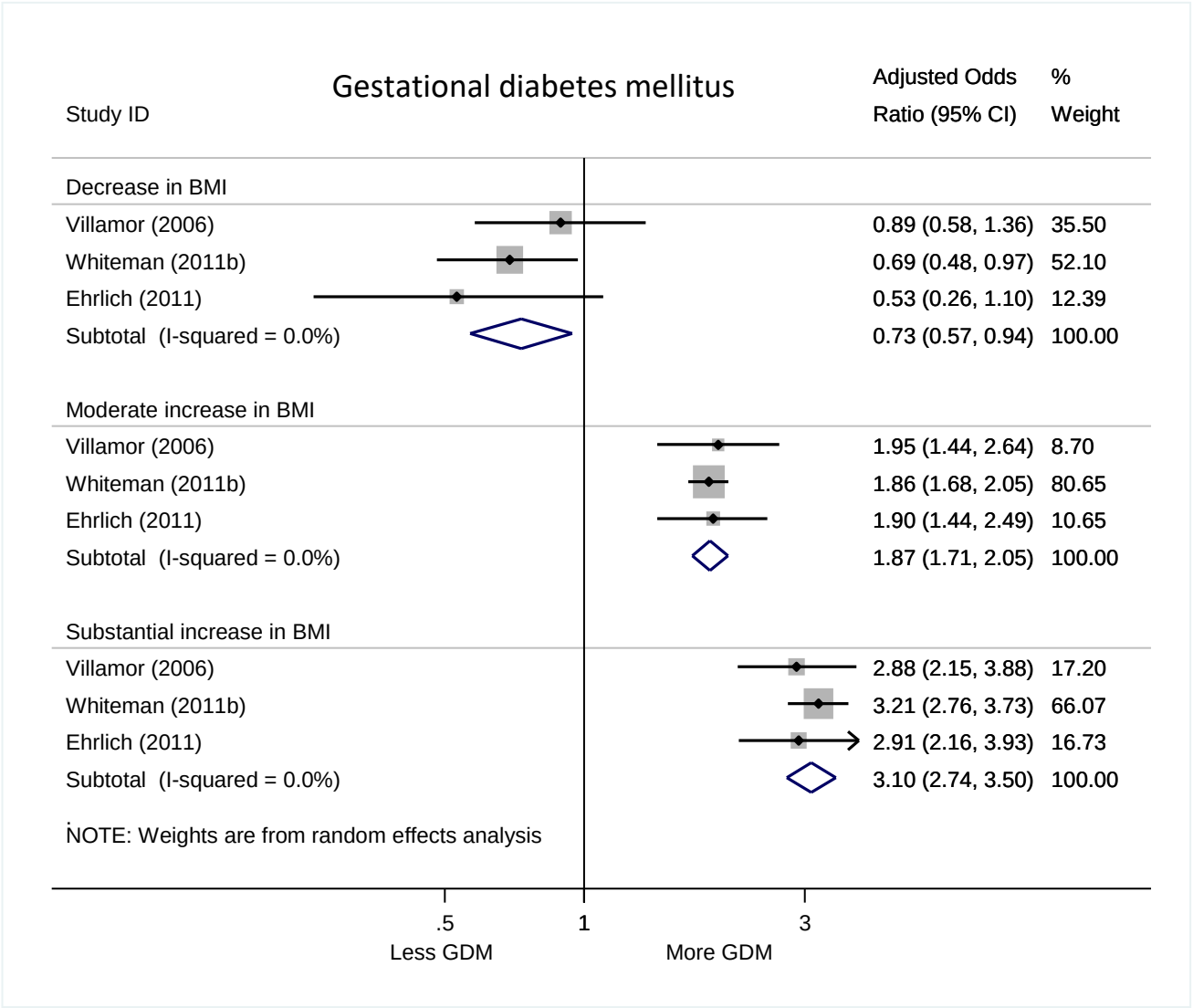

Figure 3: Forest plot showing change in interpregnancy weight and the risk of gestational diabetes mellitus in the subsequent pregnancy for women with normal BMI (< 25) at the beginning of first pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

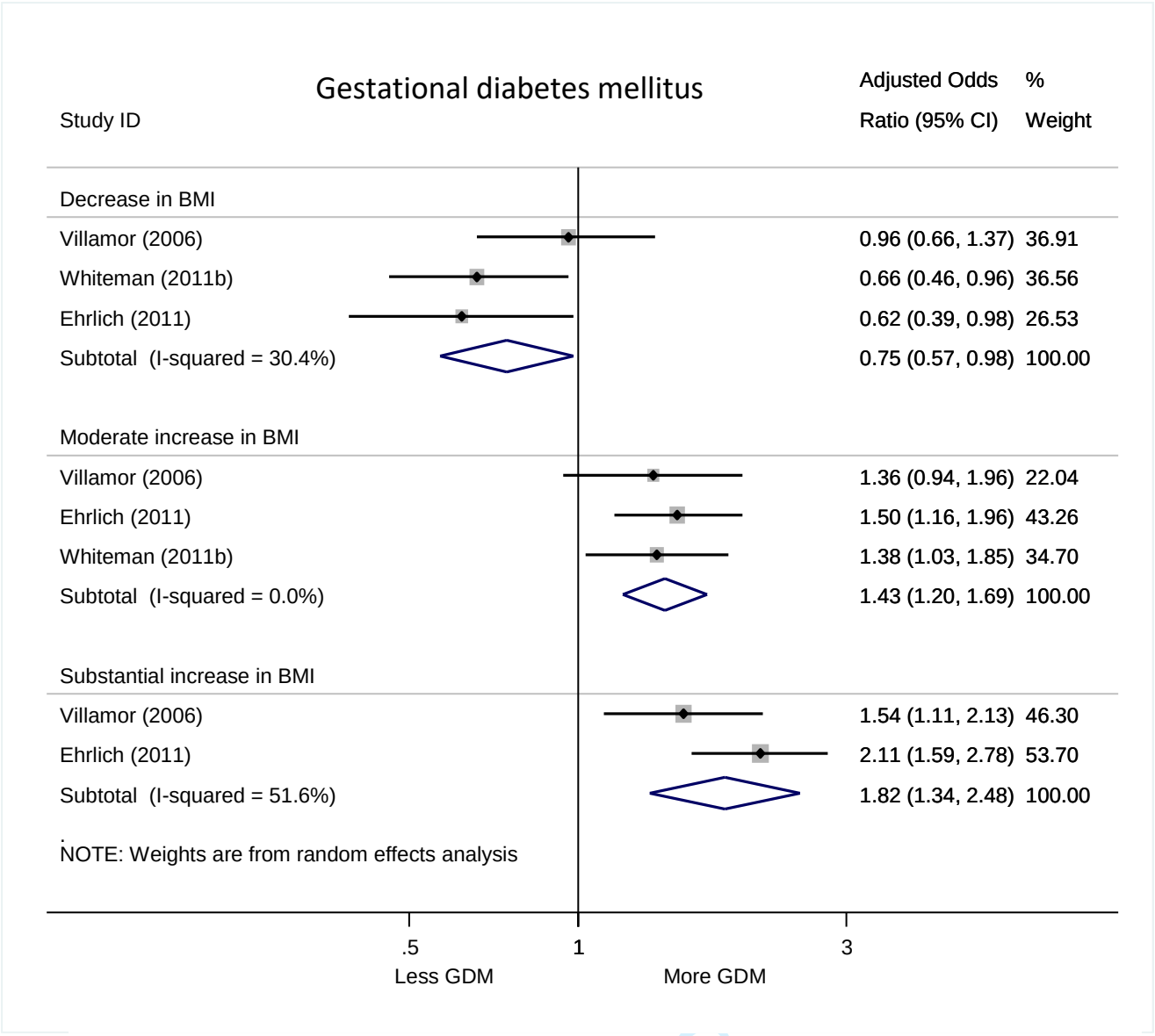

Figure 4: Forest plot showing change in interpregnancy weight and the risk of gestational diabetes mellitus in the subsequent pregnancy for women with overweight/obese BMI (≥ 25) at the beginning of first pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

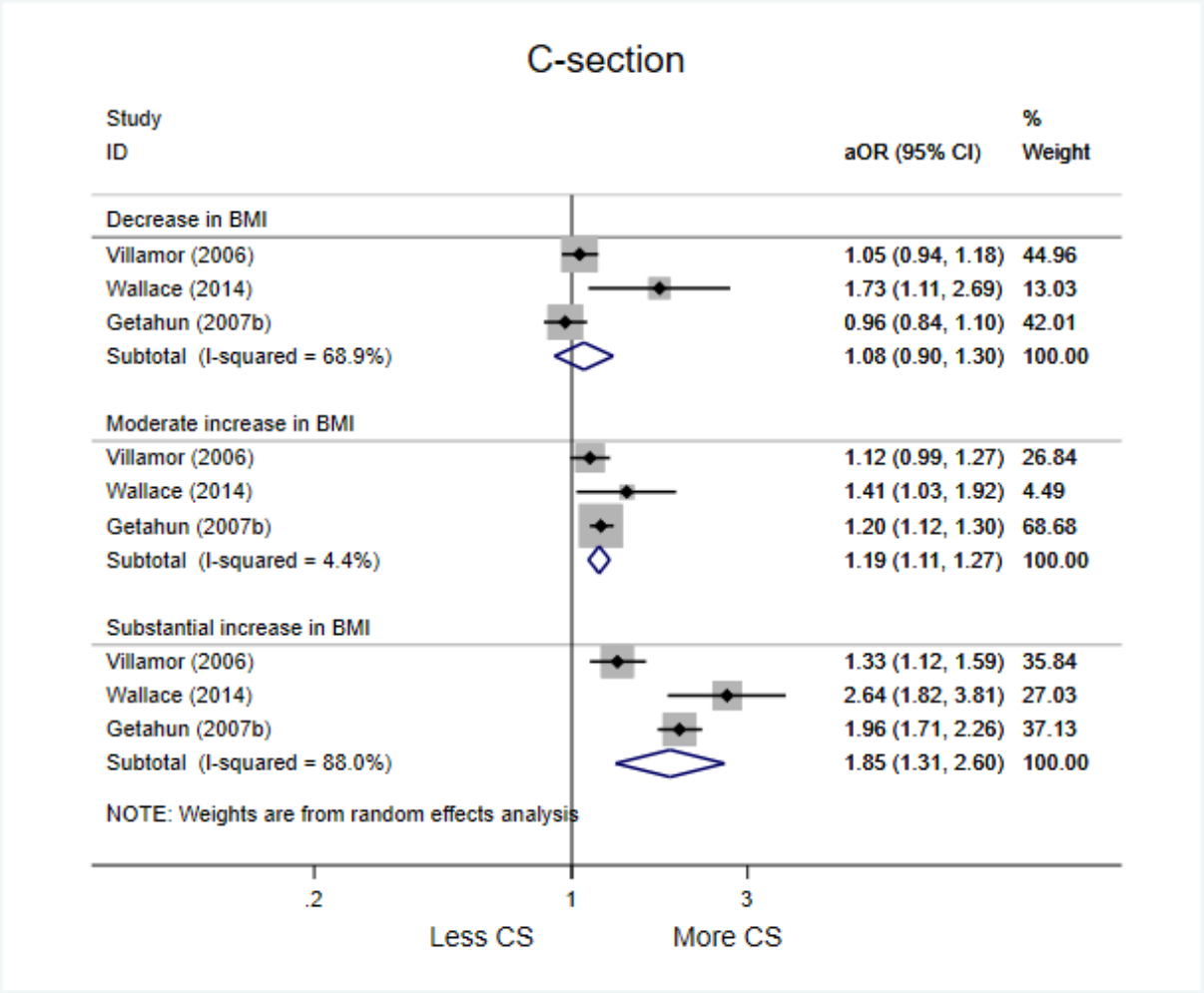

Figure 5: Forest plot showing change in interpregnancy weight and the risk of C-section in the subsequent pregnancy for women with normal BMI (< 25) at the beginning of first pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

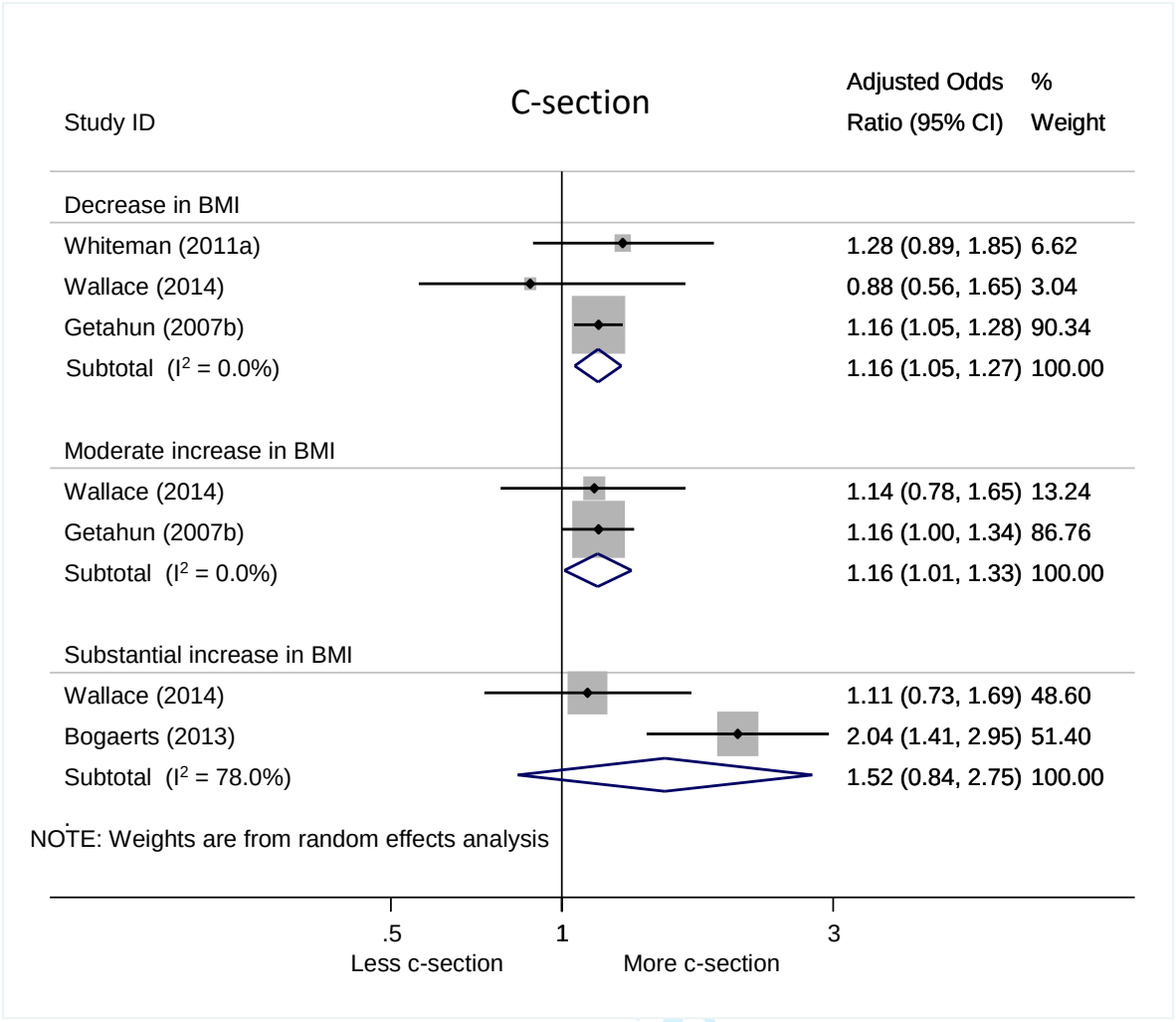

Figure 6: Forest plot showing change in interpregnancy weight and the risk of C-section in the subsequent pregnancy for women with overweight/obese BMI (≥ 25) at the beginning of first pregnancy, relative to reference category (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units, reference category remained in same BMI category or changed by up to -2 to +2 units)

APPENDIX 4

Table 1: Results after sensitivity analysis for the effect of interpregnancy BMI change on large for gestational age births, in women with a prepregnancy BMI of < 25 and ≥ 25. (Decrease in BMI defined as >-1 units, moderate increase 1 to 3 units and substantial increase > 3 units)

Prepregnancy BMI	BMI change	Number of studies	aOR (05% CI)	I^2	p-value
< 25	Decrease	2	0.63 (0.35-1.14)	77.0%	0.129
	Moderate increase	2	1.67 (1.52-1.85)	0.0 %	0.000
	Substantial increase	2	2.18 (1.94-2.44)	4.0%	0.000
≥ 25	Decrease	2	0.70 (0.47-1.02)	75.00%	0.066
	Moderate increase	2	1.16 (0.90-1.51)	22.5%	0.255
	Substantial increase	2	1.54 (1.38-1.73)	0.00%	0.000

Appendix 4 table 2: PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**2**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**3**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**3**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**4**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**4**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**4**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**4**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**4**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**4-5**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**5**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**5**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**4**
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**5**

Section/topic	#	Checklist item	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**5**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**5**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**6**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**7-8**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**Appendix 1**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**9**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**9**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**Appendix 1**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**9**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**10**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**12**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**13**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**13**

PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**2**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**3**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**3**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**4**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**4**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**4**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**4**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**4**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**4-5**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**5**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**5**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**4**
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**5**

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**5**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**5**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**6**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**7-8**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**Appendix 1**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**9**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**9**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**Appendix 1**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**9**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**10**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**12**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**13**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**13**