Maternal adiposity—a determinant of perinatal and offspring outcomes?

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Abstract | Experimental and animal data suggest that maternal obesity during pregnancy adversely affects offspring health in the short-term and the long-term. Whether these effects occur in humans and influence population health is less clear. This Review explores evidence from intervention studies and observational studies that have used designs (such as family-based comparisons and Mendelian randomization) that might help improve understanding of the causal effects of maternal obesity in humans. Collectively, human studies provide evidence that maternal overweight and obesity is causally related to pregnancy complications, increased offspring weight and adiposity at birth, and the difficulties associated with delivery of large-for-gestational-age infants. The underlying mechanisms for these effects probably involve maternal and fetal dysregulation of glucose, insulin, lipid and amino acid metabolism. Some evidence exists that extreme maternal obesity (BMI ≥40 kg/m^2) is causally related to a long-term increase in offspring adiposity, but further exploration of this relationship is needed. High gestational weight gain may result in a long-term increase in offspring adiposity if women are already overweight or have obesity at the start of pregnancy. To date, little high-quality human evidence exists that any of these effects are mediated by epigenetic mechanisms, but approaches to appropriately test this possibility are being developed.

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Introduction

In clinical practice, overweight and obesity in pregnancy are assessed at the first antenatal visit; in research practice, either this first clinical measurement or, if available, a recent prepregnancy assessment is used. These prepregnancy assessments include those obtained by retrospective self-report. Prepregnancy or early pregnancy BMI will be little affected by the pregnancy itself and, therefore, the definitions used to categorize pregnant women as having overweight or obesity are the same as those used in the general population: overweight ≥25 kg/m^2 but <30 kg/m^2; obesity ≥30 kg/m^2 but <40 kg/m^2; morbid obesity ≥40 kg/m^2. Much of the research regarding the impact of morbid obesity on perinatal and long-term offspring outcomes has been conducted in women eligible for and/or who have had bariatric surgery (including women with morbid obesity and those with a threshold BMI below that for morbid obesity, for example >35 kg/m^2, who also have obesity-related comorbidity); therefore, the term extreme obesity is used for this group throughout the Review.

The prevalence of overweight or obesity in pregnant women has increased in line with the global obesity epidemic, with up to 50% of women of reproductive age and 20–25% of pregnant women at first antenatal clinic visits having overweight or obesity in Europe and the USA.[1–3] Overweight or obesity in pregnancy is associated with an increased risk of a wide range of maternal pregnancy complications, adverse perinatal outcomes and long-term risk of overweight and obesity in the offspring.[4,5] This Review is concerned with the effect of maternal increased adiposity on adverse perinatal outcomes and long-term risk of increased adiposity in the offspring. The focus is restricted to data in humans, largely obtained from studies conducted in the past 15 years. Discussion of the extensive experimental and animal model literature related to maternal obesity is outwith the scope of the Review, and has been the subject of a number of reviews in the past 5 years.[6–9]

First, this Review outlines the evidence for an association, and also for a causal relationship, between maternal adiposity and adverse perinatal outcomes; in addition, the probable biological mechanisms underlying this relationship are reviewed. Second, evidence that maternal increased adiposity in pregnancy is causally related (via intrauterine mechanisms) to long-term risk of increased adiposity in offspring is examined. For both of these sections, data from observational studies and intervention studies are assessed, including studies aimed at reducing gestational weight gain (GWG). Finally, the possible contribution of epigenetic modification to any causal associations between maternal adiposity or GWG and short-term or long-term offspring outcomes is explored (Figure 1).

Maternal obesity and perinatal outcomes

Maternal increased adiposity is associated with almost all maternal and neonatal complications and a

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Key points

- Maternal obesity is associated with considerable maternal and fetal metabolic perturbation
- Prospective studies, including those with outcomes reported for first and second pregnancies and before and after bariatric surgery, suggest a causal association of maternal obesity with adverse pregnancy and perinatal outcomes
- Evidence also exists that extreme maternal obesity (BMI ≥40 kg/m^2) is causally related to increased adiposity of offspring during childhood and adulthood
- A dose–response effect of maternal BMI (across the whole distribution of maternal BMI) on the adiposity of offspring during childhood and adulthood is not supported by current evidence
- High gestational weight gain is weakly associated with adverse perinatal and long-term offspring outcomes; causal effects may be restricted to subgroups of the population
- Nutritional experiences related to maternal adiposity *in utero* can have effects that persist into childhood, and these effects may be mediated by epigenetic modifications, but robust causal evidence is needed

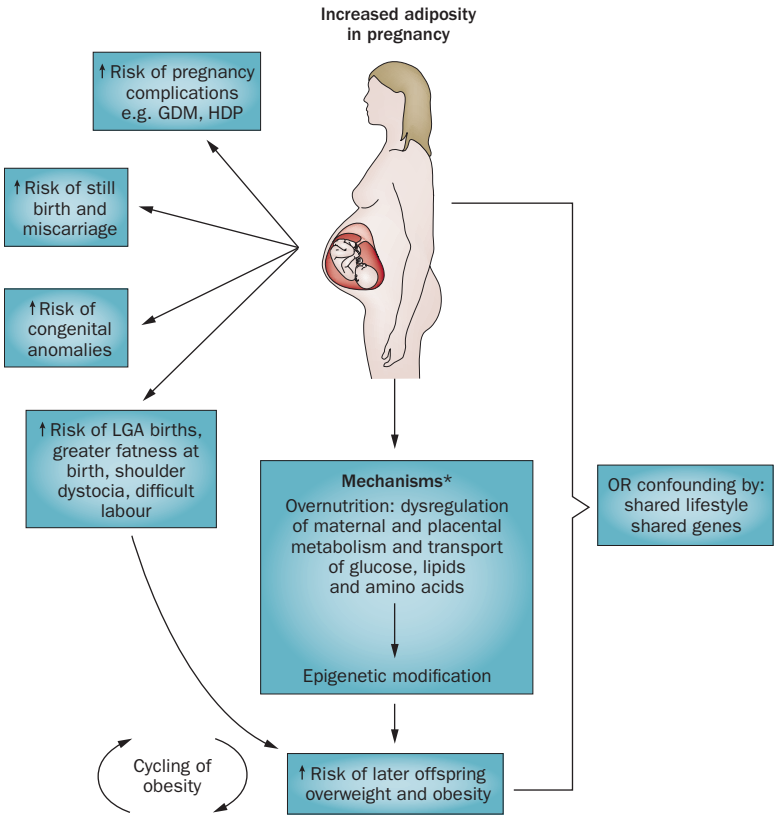

Figure 1 | Summary of the associations of maternal increased adiposity with perinatal and long-term offspring outcomes. *These mechanisms are illustrative and not exhaustive, as discussed in the Review; valid evidence for all of them is still being explored. Abbreviations: GDM, gestational diabetes mellitus; HDP, hypertensive disorder of pregnancy; LGA, large for gestational age.

multiethnic study from the Netherlands suggests that it now exceeds maternal smoking as the lifestyle-related risk factor that is believed to cause the greatest proportion of adverse pregnancy outcomes.[10] To randomly allocate women to different levels of adiposity before pregnancy is clearly not feasible. However, the validity of the hypothesis that maternal increased adiposity is the causal factor that underlies adverse maternal and perinatal outcomes has been strengthened by several epidemiological observations.

First, a graded, positive linear (dose–response) association exists between an increase in BMI between first and second pregnancies and an increase in the risk of pre-eclampsia, gestational hypertension, caesarean delivery, stillbirth and large-for-gestational-age infants between first and second pregnancies.[11–13] Second, the risk of adverse pregnancy outcomes is reduced in previously extremely obese women who have undergone bariatric surgery compared with those who have not undergone surgery.[14] Importantly, analysis of outcomes in women who had a pregnancy before and another one after bariatric surgery revealed a reduction in the prevalence of hypertensive disorders, gestational diabetes mellitus (GDM), infants with high birthweight, and macrosomia after bariatric surgery.[15,16] The data from these analyses are unlikely to be explained by confounding by, for example, socioeconomic position or indication for surgery, as the same woman is used as her own matched control. Moreover, clear causal mechanisms linking obesity levels to metabolic dysregulation and thus increased risk of diabetes mellitus are well established in the general (male and female nonpregnant) population and it seems implausible that these would not hold in the situation of pregnant women.

Mechanisms for perinatal effects

The pathophysiological mechanisms underlying the increased risk of adverse perinatal outcomes in pregnant women with obesity is not fully understood. Increased insulin resistance, hyperglycaemia and hyperinsulinaemia, as observed in the general population with obesity, are likely to contribute to the increased risk of GDM and may contribute to other adverse perinatal outcomes.[17] However, maternal obesity is associated with other adverse pregnancy and perinatal outcomes independently of GDM.[17] This independence of association means that any woman who has both obesity and GDM will have a greater risk of pre-eclampsia, large-for-gestational-age infants, high infant fat mass at birth and elevated cord C-peptide levels (a marker of fetal insulin secretion) than a woman with just one of these two risk factors.[17]

Dysregulation of glucose, insulin, lipid and amino acid metabolism could plausibly have a role in the effect of maternal increased adiposity on pregnancy complications and adverse perinatal outcomes. The transplacental passage of circulating glucose is principally accomplished by facilitated diffusion, with a high capacity that becomes saturated only at levels ≥20 mmol/l.[18] Even small changes in the level of glucose in the maternal circulation will, therefore, be transmitted to the fetus. Consistent with this potential mechanism, pregnant women with obesity who have normal glucose tolerance still have higher daytime and nocturnal glucose profiles than normal-weight pregnant women, thereby exposing the fetus to relative hyperglycaemia.[19] Although the relationship of maternal glucose levels with fetal growth is continuous, the high strength of the independent relationship of maternal obesity with fetal hyperinsulinaemia, birthweight and neonatal adiposity suggests that additional

factors, plausibly including lipids and amino acids, may also contribute.

Blood lipids, in particular triglycerides, increase to reach peak levels at 31–36 weeks gestation in response to gestational hormones—progesterone, 17β-oestradiol and placental lactogen—in normal pregnancy (in women across the whole range of adiposity).[20,21] In pregnant women with obesity, elevation of triglyceride levels and a concomitant transient reduction in levels of HDL cholesterol is particularly marked.[22] The transplacental transport of lipids is not fully understood; however, in women with maternal obesity and gestational hyperlipidaemia, normal placental lipid transport and synthesis might be disrupted, which could influence fetal growth and development.[23]

With respect to amino acids, measured protein synthesis does not increase in the first trimester in pregnancies in normal-weight women, but increases do occur in the second and third trimester, of 15% and 25%, respectively.[24–27] How maternal obesity affects these changes in protein synthesis during pregnancy is unknown, but in nonpregnant women with obesity there is an attenuated protein anabolic response consistent with insulin resistance,[28] and it seems plausible that this attenuated response also occurs in women with obesity during pregnancy. Obesity in the general, nonpregnant population is also associated with an increased supply of gluconeogenic amino acids to the liver, with preference of their use over glycogen for glucose production.[29]

One small study of nonselected pregnant women found that visceral lean body mass is positively correlated with maternal protein turnover that, in turn, is associated with increased birth length.[30] Collectively, data suggest that the anabolic response to pregnancy is impaired in women with obesity, which raises the possibility that some aspects of fetal growth, for example growth of skeletal or lean mass, are limited as a response to maternal obesity.

With respect to transport of proteins across the placenta, the SLC38 family of sodium-dependent transporters, which are responsible for amino acid transport and are mainly expressed in the central nervous system, are also expressed in the placenta and influence fetal growth.[31,32] Decreased activity of system A transporters (SNAT1, SNAT2 and SNAT4, also known as SCL38A1, SCL38A2 and SCL38A4, respectively) is associated with fetal growth restriction. Evidence in the past few years has shown that in pregnant women with obesity (BMI 30–40 kg/m^2), placental system A SNAT activity is decreased.[31] This decreased activity was contrary to the hypothesized direction of association, which was that placental SNAT activity would be increased, and hence might mediate the association of maternal obesity with large-for-gestational-age infants. The authors of the study speculated that this unexpected direction of association might have been because participants with obesity achieved the recommended GWG in this study.[31] That reduced placental SNAT activity in pregnant women with obesity might mediate the hypothesized reduction in lean mass in infants born to mothers with obesity is also possible.

That the placenta actively responds to the maternal environment is not a new concept. Evidence exists that maternal increased adiposity is associated with placental ultrastructural changes, accumulation of maternal macrophages, and increased placental weight, vascular muscularity and expression of inflammatory cytokines.[33–37] Together this evidence raises the possibility of an adaptive, but also potentially pathological, placental response to excessive nutrient supply of the type that occurs in women with increased adiposity. This placental response could help to explain the adverse short-term and long-term outcomes of offspring from mothers with obesity.

GWG and adverse perinatal outcomes

Despite evidence for an adverse effect of increased maternal adiposity on a wide range of pregnancy and perinatal outcomes, preconceptional optimization of weight is difficult to achieve at a population level. In the UK, for example, 50% of pregnancies are unplanned. Furthermore, even in women planning a pregnancy, only a small proportion will follow nutritional and lifestyle recommendations.[38] This fact potentially limits the efficacy of a prepregnancy intervention and, consequently, focus has shifted to pregnant women themselves and limiting their GWG.[39,40] Evidence about the effect of GWG has come largely from observational studies to date, although some intervention studies aimed at limiting weight gain have also been conducted.

The total amount of weight gained in normal term pregnancies varies considerably among women and is related to the number of fetuses (singleton pregnancy 10.0–16.7 kg, twin pregnancy 15–22 kg, triplet pregnancy 20.5–23.0 kg), ethnicity, maternal age and parity, and is inversely correlated with prepregnancy BMI.[39] Observational studies have consistently demonstrated that both low and high GWG are associated with a number of adverse pregnancy and perinatal outcomes.

Moderate to strong evidence exists for low GWG being associated with preterm birth, low birthweight and small-for-gestational-age infants, and strong evidence exists for the association of high GWG with high birthweight, macrosomia and large-for-gestational-age infants.[39] To some extent these associations are probably driven by the relationship of fetal growth to GWG and final birth size. No good evidence exists of associations between GWG and neonatal hypoglycaemia, neonatal distress, hyperbilirubinaemia, neonatal hospitalization or other infant morbid conditions.[39] For maternal outcomes, the positive association of GWG with risk of Caesarean section is likely to be confounded by pre-pregnancy BMI and concurrent medical disorders such as GDM.[39] The strength of evidence for an association of GWG with the major forms of pregnancy complications, such as GDM and hypertensive disorders of pregnancy, is weak; however, consistent evidence exists of an association of high GWG with short-term and long-term postpartum weight retention.[39]

Of importance, when GWG has been assessed as compliant with guidance from the 2009 Institute of Medicine (IOM) guidelines on GWG (Table 1),[40] the associations

Table 1 | US IOM guidelines for gestational weight gain[40]

Prepregnancy BMI	Recommended range of absolute weight gain (kg)
Underweight <18.5 kg/m^2	12.5–18.0
Normal weight 18.5–24.9 kg/m^2	11.5–16.0
Overweight 25–29.9 kg/m^2	7.0–11.5
Obese ≥30 kg/m^2	5.0–9.0

Note the recommendations allow different amounts of weight gain depending upon the woman's prepregnancy BMI. Abbreviation: IOM, Institute of Medicine.

of GWG with many maternal and perinatal outcomes are attenuated and restricted to specific subpopulations.[39,40] For example, GWG above that recommended by the IOM is associated with increased birthweight and macrosomia, but this association is restricted only to women who had underweight or normal weight at the start of pregnancy.[39,40] GWG below that recommended by the IOM was strongly associated with the risks of preterm birth, low birthweight and having a small-for-gestational-age infant.[39,40] As noted above, these associations, whilst robust, are likely to be driven by the clear effect of fetal growth and length of gestation on total GWG and these outcomes (namely, fetal growth restriction will result in lower GWG and low birthweight, whereas short gestation will limit the time for increased GWG and also be related to preterm birth). The question remains whether continued monitoring of maternal weight during pregnancy could identify women at increased risk of adverse outcomes sufficiently early for appropriate preventive interventions to be effective.

Although the systematic review that was used to inform the IOM recommendations included a large number of sizeable longitudinal studies, it yielded little in the way of consistent findings because, as the authors noted, the body of research lacked methodological rigor, precision and directionality.[39] Major shortcomings included the lack of uniformity in definitions of exposure and outcomes, lack of structured and transparent approaches for assessing confounders and effect modification, lack of power to detect meaningful differences, and inadequate approaches for assessing multiple outcomes related to GWG for the mother and child. Furthermore, many of the studies failed to provide a conceptual model that accounted for physiological processes, which would have enabled the identification of pre-existing maternal conditions that could confound the relationship between GWG and outcomes. Despite these limitations, GWG has become a focus of clinical policy for pregnant women in the USA and some other countries. In the USA, GWG recommendations are included in policy for all pregnant women (irrespective of their BMI), in other countries the focus is only on women who are overweight or have obesity.

Randomized controlled trial evidence in this area is limited. A systematic review and meta-analysis of the effects of maternal pregnancy lifestyle interventions on GWG found evidence that such interventions effectively reduce maternal GWG (reduction of 1.42 kg, 95% CI 0.95–1.89); interventions that were dietary only were particularly effective.[41] In the same meta-analysis, the effect of interventions that limit GWG on maternal and perinatal outcomes was explored. These interventions reduced infant birthweight and pre-eclampsia; however, for the other outcomes, including GDM, preterm delivery, Caesarean section and postpartum haemorrhage, pooled point estimates suggested weak beneficial effects, but confidence intervals were wide and included the null value.[41] The effect on pre-eclampsia of lifestyle interventions that limited GWG could, however, be explained by the treatment of GDM that occurred in the two largest studies contributing to the meta-analysis.[42,43]

In sensitivity analyses, some evidence existed that the reduction in GWG was greater, but the reduction in birthweight was smaller, in women who were overweight or had obesity compared with those who had normal weight or were underweight, but other outcomes did not vary by maternal BMI.[41] These latter results are consistent with those of another systematic review.[44] Importantly, the majority of studies included in both of these systematic reviews were rated as having low or modest levels of quality and were small, with ≤100 participants.[41,44] Thus, to date, the beneficial effects on pregnancy outcome of attempts to modify maternal lifestyle, and by these interventions limit GWG, are unclear. A number of large, lifestyle intervention trials in pregnant women are ongoing and the results of these studies will be key to clarifying this important question.

Mechanisms for perinatal GWG effects

To date, a paucity of research has investigated the mechanisms that might underlie associations of GWG with obstetric and perinatal outcomes. In all such research, a clear difficulty exists in separating out the effects of different components of GWG (such as maternal fat deposition, volume expansion, placenta, fetus and amniotic fluid). The underlying mechanisms for the relationship of GWG with both short-term and long-term offspring outcomes (discussed below) is assumed to be driven by the same mechanisms as those described above for maternal obesity. Thus, the component of GWG that is potentially most important causally is maternal fat deposition.

Long-term outcomes of offspring

Developmental overnutrition, resulting from maternal overweight or obesity, could contribute to the current obesity epidemic and continue to exacerbate the problem across many generations even if effective obesity prevention started today.[45–47] Proponents of this hypothesis argue that increased maternal adiposity is related to incremental increased maternal metabolic impairment that results in overnutrition of the developing fetus; in consequence, the offspring is set on a trajectory of increased adiposity throughout life, owing to increased adiposity at birth or effects on the developing neuroendocrine, pancreatic, hepatic or musculoskeletal systems.[45–48] Female offspring with increased adiposity who subsequently become pregnant will translate the cycle of developmental overnutrition across generations.[45–48]

Findings of a large number of observational studies show that maternal and offspring adiposity are positively and incrementally associated.[49] However, observational studies are unequipped to distinguish genetic or postnatal environmental explanations from a truly causal intrauterine mechanism.[49,50] For this reason, this part of the Review focuses on studies that better enable this distinction. In within-sibling comparisons, a causal intrauterine effect would be supported if the long-term adiposity of offspring was greater in the sibling born when the mother had more adiposity than in the one born when the mother had less adiposity; such differences would not be explained by maternal genotype, which would be identical for each sibling, and would be less likely than in conventional observational studies to be confounded by background familial socioeconomic or lifestyle characteristics that are often similar between siblings who are close in age.[49,50] Furthermore, stronger associations between maternal adiposity and offspring adiposity than between paternal adiposity and offspring adiposity would be anticipated if intrauterine mechanisms explain the association. Similar associations of maternal and paternal adiposity with offspring adiposity would support shared familial genetic or (postnatal) lifestyle inheritance than a specific intrauterine mechanism.[49,50] Mendelian randomization studies refer to the use of genetic variants that are robustly associated with the exposure of interest (for example, maternal pregnancy adiposity) as proxies (instruments) to determine the unconfounded and unbiased effect of the exposure on outcomes (for example, offspring adiposity).[51]

Evidence from within-sibling and between-parent comparisons in the Pima Indians of Arizona suggests that GDM is causally related to long-term offspring risk of increased BMI and that intrauterine mechanisms, over and above shared genetic and postnatal environmental characteristics, have a causal role in this association.[52] Within-sibling comparisons in a lean European population support these conclusions.[53] As maternal overweight and obesity is a risk factor for GDM, these findings provides some support for a causal effect of maternal increased adiposity on long-term offspring outcomes, but this effect needs to be explored directly.

Effects of maternal extreme obesity

In two studies, offspring of mothers with extreme obesity born before and after their mothers had experienced marked weight loss following gastric bypass surgery were compared with respect to BMI and related cardiometabolic outcomes.[15,54] Offspring were aged 2–18 years at assessment in both studies. In the first study, 45 children born to 34 women before bariatric surgery (when they had a mean BMI of 48 kg/m^2) were compared with 172 children born to 113 women (including the 34 women mentioned above) after their surgery when their mean BMI was 3 kg/m^2.[54] The prevalence of overweight and obesity was increased and that of normal weight and underweight was decreased in the children born before their mothers' surgery. These differences in offspring weight between the before-surgery and after-surgery groups remained when analyses were restricted to within-sibling comparisons.[54]

In the second study by the same group of researchers, the weight of 54 children born before gastric bypass surgery and 57 born after surgery was compared. This study also included a nested within-sibling study of 37 siblings born before surgery and 38 after surgery to 25 mothers. Both in the whole study population and the within-sibling study, children born to mothers' before they had surgery for extreme obesity, compared with those born after the mothers' surgery, had higher mean BMI and prevalence of overweight or obesity; the offspring of before-surgery mothers also had an increased body fat percentage and waist-to-hip ratio, and increased levels of fasting insulin, glucose and triglycerides and reduced HDL cholesterol levels.[15] In both of these studies for the within-sibling part of them, the average age between the siblings was 2 years; therefore, a lifestyle difference between siblings is unlikely to explain the observed differences in outcomes. Some of the observed difference in outcomes of the before-surgery and after-surgery offspring could have been due to the reduced GWG of the mothers after surgery.[15]

Maternal adiposity—incremental effects

From a public-health perspective, an incremental effect of maternal adiposity (across the whole distribution) on offspring outcomes would have a much larger impact than an effect only in extreme maternal obesity and would be a more plausible driver of the obesity epidemic, as the proportion of women entering pregnancy with a BMI ≥40 kg/m^2 still remains low. Furthermore, a linear association of maternal BMI and other measures of adiposity with risk of glucose intolerance exists, and of glucose intolerance with increased offspring birthweight and cord blood C-peptide levels; therefore, one might anticipate an incremental effect of maternal BMI on offspring outcomes across the whole distribution of BMI.

Findings of a large number of observational studies show that maternal and offspring adiposity are positively and incrementally associated. However, as discussed above, observational studies are ill-equipped to distinguish genetic or postnatal environmental explanations from a causal intrauterine mechanism.[49,50] Focus has, therefore, been directed at the findings of studies that are better able to distinguish causal intrauterine mechanisms from confounding. Evidence from studies that have compared the association of maternal and paternal BMI (across the whole distribution) with offspring adiposity is conflicting. Some studies have found stronger associations of offspring adiposity with maternal BMI than with paternal BMI, although the differences in the magnitudes between the maternal and paternal associations in these studies are modest.[55–57] In the largest studies to date, the magnitudes of associations of maternal BMI with offspring adiposity are similar to those of paternal BMI with offspring adiposity,[58–61] which suggests that these associations are driven by shared familial genetic or lifestyle characteristics.

A large Swedish within-sibling comparison study found that maternal early pregnancy BMI was positively

associated with offspring BMI in the whole cohort and between nonsiblings, but not within siblings.[53] These results suggest that the association between maternal BMI and offspring BMI observed in the cohort as a whole, and also in other studies that have not used a sibling comparison, might be explained by confounding owing to characteristics that are identical or very similar between siblings, such as maternal genotype, socioeconomic position, diet and patterns of physical activity.

A Mendelian randomization study was conducted in which maternal genetic variation in the *FTO* gene (conditional upon offspring *FTO* genotype) was used as an instrumental variable[51] to estimate the causal effect of exposure to increased maternal adiposity *in utero*.[57] The study did not provide support for incremental differences in maternal BMI in pregnancy causally affecting offspring adiposity.[57] However, the instrumental variable analysis result was imprecisely estimated, with very wide confidence intervals, and replication of this study in a large cohort or with multiple genetic variants related to adiposity is needed.[57]

GWG—incremental effects

Several studies have found positive associations of GWG with measures of offspring adiposity in childhood,[62–65] adolescence[66] and adulthood.[67,68] Most of these studies used fairly crude assessments of GWG, which were usually based on just two measurements near the start and end of pregnancy, with at least one of these being self-reported.

Some of the approaches that might be used to improve causal inference in observational epidemiology are not possible with GWG. For example, whilst partners of pregnant women may gain weight when their partner is pregnant, few, if any, studies monitor paternal weight gain; therefore, comparing maternal to paternal exposure to see if a specific maternal association exists is not currently possible. To date, genetic variants that are robustly associated with variation in GWG and that could be used as instrumental variables to examine the causal association of GWG with long-term offspring adiposity in Mendelian randomization studies have not been identified. Genetic variants that are robustly associated with maternal and offspring adiposity appear not to be associated with GWG.[69]

Two published studies have used more valid methods for assessing a causal effect of GWG on offspring adiposity in childhood or adulthood.[65,70] In a UK birth cohort (n = ~12,500 pregnant women) repeated measures of weight in pregnancy were used to examine whether a specific association exists between GWG in early pregnancy (up to 18 weeks gestation) and long-term offspring adiposity and related cardiometabolic outcomes.[65] The findings suggest that GWG in early pregnancy is linearly, across the whole distribution, positively associated with offspring adiposity. GWG in mid pregnancy (18–28 weeks) was also positively associated with offspring adiposity, but only in women who gained >500 g per week, and after 28 weeks no clear association of GWG with offspring outcomes was found.[65] As maternal fat deposition contributes more to GWG in early pregnancy (with fetal, placental and amniotic fluid contributing more in late stages of pregnancy),[71] these findings provide tentative evidence that maternal fat accretion early in pregnancy drives the associations of GWG with long-term offspring adiposity.

A large Swedish sibling comparison study examined the association of maternal weight retention with offspring BMI at age 18 years.[70] In the within-sibling analysis, no evidence of an association was found in mothers with a normal prepregnancy weight; however, amongst overweight and obese mothers, greater weight retention was associated with greater offspring BMI.[70] This study has advantages over other studies. First, the study has a within-sibling design and, second, it uses a measure of weight gain in the mother during pregnancy that does not including amniotic fluid, placenta and fetal contributions. The findings suggest that amongst normal-weight women, the positive association of GWG with long-term offspring BMI found in other studies is driven largely by shared familial (genetic and/or environment) risk factors. By contrast, in women who are overweight or have obesity in early pregnancy, GWG might be positively associated with long-term offspring BMI via intrauterine mechanisms in addition to shared familial characteristics. These results are consistent with findings in the bariatric surgery studies described above, which suggested that observed difference in outcomes between the before-surgery and after-surgery offspring might in part have been due to the reduced GWG in women with extreme obesity after they underwent bariatric surgery.[15]

An editorial published this year noted that preliminary results from a study in which the effects of different components of GWG were separated indicated that fetal weight gain was the primary GWG predictor of child BMI, whereas a mother's tissue gain was the only predictor of her own postpartum weight retention.[72] The findings described in this editorial that relate to maternal postpartum weight retention have been published as a conference abstract,[73] but those related to child BMI are, as yet, unpublished.

Long-term offspring outcome—mechanisms

The above review of evidence from human studies supports causal associations of maternal extreme obesity, and possibly of high GWG (particularly in women who are overweight or have obesity), with offspring increased adiposity in childhood and adulthood. In this section, possible mechanisms in relation to these two exposures are discussed. As this Review is concerned with evidence from human studies, mechanistic studies in human populations were identified. Animal models have been used to examine developmental programming effects of maternal overnutrition on specific physiological pathways, and suggest a role for developmental programming effects on multiple systems, including the hypothalamus and its associated neuroendocrine system (which influences appetite), the musculoskeletal system and the liver and pancreas (which influence insulin resistance and glucose homeostasis), and on systems related to oxidative

stress.[8,9,74] However, these specific mechanisms have not been directly assessed in human studies to date.

High GWG will be influenced by fast fetal growth, which will result in high birthweight, and extreme maternal obesity results in overfeeding of the developing fetus. Thus, both high GWG and extreme maternal obesity result in offspring with high birthweight. Total weight and adiposity track through life (someone who has high weight and adiposity at birth will, on average, remain so throughout life), with birthweight being positively associated with long-term offspring lean and fat mass.[75] Therefore, the key mechanism underlying the association of high GWG and maternal extreme obesity with long-term offspring increased adiposity could be that both result in large infants at birth who then on average stay large throughout life.

With respect to extreme obesity and the associated increased risk of GDM, intrauterine overnutrition results in increased adiposity at birth and specific tracking of adipose tissue could occur across life (namely, infants born with an increased number of adipocytes continue to have an increased number through childhood and adulthood). Evidence against this suggestion is the fact that most studies of the associations of GDM, extreme maternal obesity or GWG with offspring adiposity find little evidence that birthweight is a major mediator of the association. However, measurement errors in birthweight in these studies, and/or a failure to fully account for all potential confounding factors (namely, failure to fully account for confounding between maternal extreme obesity and birthweight or adiposity and, secondly, between birthweight or adiposity and long-term offspring adiposity) could mean that these studies are unable to validly test the hypothesis.

Mediation by epigenetic modifications

Epigenetic mechanisms are increasingly proposed as key mediating mechanisms in the developmental origins field in general, and specifically in relation to developmental overnutrition. These mechanisms could mediate some of the short-term and long-term effects of maternal obesity and GWG discussed throughout this review. Epigenetics refers collectively to several factors that regulate gene expression, the most commonly studied of which is DNA methylation. Environmentally responsive, mitotically stable epigenetic phenomena, such as DNA methylation, could potentially provide a plausible mediating mechanism for the developmental origins of disease, including developmental overnutrition, especially as a large body of literature attest to the influence of nutrition on the epigenome.[76]

Although an effect of epigenetic mechanisms has been reported in studies of animal models of developmental overnutrition,[74,77] few human studies have provided empirical supporting evidence of a direct link between maternal exposures, neonatal or childhood epigenetic variation and subsequent phenotypic differences. Exposure to the Dutch famine *in utero* was associated 60 years later with differences in peripheral blood DNA methylation at the *IGF2* locus, when compared to that of same-sex siblings who were not exposed to the famine *in utero*.[78] Furthermore, rural Gambians who had markedly different periconceptional nutrition, related to season of conception, had differences in DNA methylation patterns in peripheral blood at metastable epialleles (areas of the DNA in which methylation is likely to be stable for different tissues and cells) in childhood (mean age 6.6 years; range 3–11 years).[79]

Lastly, in a study of 23 women at term with impaired glucose tolerance (assessed at 24–28 weeks gestation) and 25 age-matched and BMI-matched women at term with normal glucose tolerance, no significant difference in DNA methylation of the leptin gene in placental tissue was found between the groups.[80] However, in women with impaired glucose tolerance (but not in those with normal tolerance) there was an inverse correlation of 2-h postload glucose levels with fetal-side placental tissue leptin gene DNA methylation and a positive correlation with maternal-side placental tissue leptin gene DNA methylation.[80] The authors acknowledged they were unclear why this association should differ between maternal-side and fetal-side placental tissue, and acknowledged their findings required further replication.

Whilst these finding are interesting and suggest that different nutritional exposures *in utero* influence placental DNA methylation and long-term term differences in methylation patterns at different genetic sites, alone they do not provide evidence that these associations are causal or that DNA methylation status is an important mediator between maternal obesity (or other related influences on nutritional exposures *in utero*) and pregnancy outcomes or long-term offspring outcomes. Further research would need to show that these epigenetic modifications influenced protein expression, that the changes to this expression influenced obstetric and/or offspring outcomes in later childhood and/or adulthood, and that each of the associations in the chain were causal, as opposed to being explained by confounding or reverse causality. To date, we are not aware of any evidence that has been provided for all of these steps.

In one study, the degree of DNA methylation of the promoter regions of five candidate genes—*RXRα*, *eNOS*, *SOD1*, *IL8* and *PI3KCD*—in umbilical cord tissue was positively correlated to DXA-determined fat mass at age 9 years in an initial cohort of 78 children; however, only the positive correlation of the degree of methylation of *RXRα* with fat mass of children was replicated in an independent cohort of 239 children of 6 years of age.[81] In the same study, maternal-reported carbohydrate intake at around 18 weeks gestation was inversely correlated with the degree of DNA methylation of the promoter region of *RXRα*.[81] These two associations do not clearly fit the developmental overnutrition hypothesis, as one might expect increased maternal energy intake to be associated in the same direction with the degree of DNA methylation of the *RXRα* promoter, as it is with later offspring adiposity. In a second study, DNA methylation status at 24 candidate gene sites in cord blood samples was related to a range of anthropometric outcomes. Differential methylation at five sites was associated with offspring BMI and/or

fat mass at age 9 years, but none of these associations withstood adjustment for multiple statistical tests.[82]

One way of examining causation in this area is the use of genetic variants that are robustly associated with the environmental exposure of interest (for example, maternal adiposity or glucose intolerance) and *cis* genetic variants that are robustly associated with DNA methylation in a two-step Mendelian randomization design.[83] A study using this approach to examine whether DNA methylation and gene expression causally mediated the association between rapid, early postnatal growth and later adiposity found little supportive evidence,[84] but to date this promising approach has not been applied widely to the field of developmental overnutrition.

Importantly, epigenetic signatures are tissue-specific and the reliance of epidemiological studies on easily accessible sources of DNA (such as cord or peripheral blood)[85] could limit the capacity to decipher important epigenetic changes in target tissues such as adipose tissue, liver, pancreas, muscle or brain. An important contribution can be made by animal studies in this regard, as these target tissues can be more readily interrogated for evidence of epigenetic perturbation than in human studies.

Future research needs

Future research must integrate different disciplines, including basic and population science, with bidirectional translation between the two, and also to integrate different study designs within and between disciplines. This future research should include the long-term follow-up of participants in ongoing, large randomized controlled trials that aim to limit weight gain and/or improve diet or activity levels in pregnant women with obesity or overweight. These trials have been established to assess the effect of interventions on perinatal outcomes; however, they provide an unprecedented opportunity to examine causal intrauterine mechanisms related to developmental overnutrition and assess whether lifestyle modification and pharmacological treatment (as appropriate) are effective in reducing long-term adverse outcomes in offspring.

To realise this objective, trial investigators need to be prepared to work collaboratively across trials, as few of even the large trials involving 1,000–2,000 participants will have adequate statistical power alone to precisely estimate long-term effects on offspring. Trial investigators will also need to be persuaded of the value of adding measurements that can assess probable underlying causal mechanisms, including assessment of glucose and lipid metabolism during pregnancy, detailed repeat scans of fetal growth *in utero*, and epigenetic signatures in mothers and offspring (including in different tissues, for example placenta, cord and blood).

Findings from these trials need to be integrated with research in large population cohorts that use methods such as family-based comparisons and Mendelian randomization to test causal effects of different levels of maternal adiposity and GWG on short-term and long-term offspring outcomes. Including epigenetic data in such studies and using a two-stage Mendelian randomization approach to explore whether epigenetic modification mediates any causal effects is also needed. Importantly, findings from both intervention and observational population studies should be triangulated with those from basic science and animal-based studies (particularly in regard to epigenetic modification studies, for which tissue-specific analyses are difficult in large-scale human studies).

Lastly, research of novel public-health initiatives aimed at preventing obesity or improving lifestyles in the whole population are of paramount importance. Targeting young women, particularly when they are beginning to consider having a family, has potential additional benefits as overweight and obesity is a major contributor to infertility.

Conclusions

Some robust evidence exists that maternal overweight and obesity is causally related to pregnancy complications, increased birthweight and offspring adiposity and the associated difficulties with delivery of large-for-gestational-age infants. The underlying mechanisms for these effects probably involve dysregulation of glucose, insulin and lipid metabolism. Evidence also exists that extreme maternal obesity may be causally related (via intrauterine mechanisms) to increased offspring adiposity in the long-term, but further exploration of these processes is required. A dose–response association across the whole distribution of maternal BMI with long-term adiposity of offspring is not supported by current evidence and, as such, population-level increases in maternal BMI across the whole BMI distribution are unlikely to be driving the current obesity epidemic. High GWG may be associated with adverse pregnancy outcomes and short-term and long-term offspring outcomes, but these associations may be limited to specific subgroups and require further replication. Epigenetic mechanisms might mediate some associations of maternal overweight or obesity and GWG with offspring short-term and long-term outcomes. Currently, little high-quality, human evidence exists for this role of epigenetics, but this area of research is in its infancy and approaches to appropriately test such causal mechanisms are under development.

Review criteria

The authors examined studies that have used a variety of epidemiological approaches designed to improve causal inference, including family-based studies and Mendelian randomization studies. The multidisciplinary team's knowledge of this field was complemented by systematically searching for and reviewing published literature in the areas of maternal obesity, gestational weight gain and the effects of these factors on perinatal and offspring outcomes. To this end, PubMed was searched for full-text articles in the English language published up to July 2012 using the MeSH terms "obesity" and "pregnancy".

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Author contributions

All authors researched data for the article and reviewed and/or edited the manuscript before submission. D. A. Lawlor and S. M. Nelson provided a substantial contribution to discussion of the content and D. A. Lawlor wrote the manuscript.