Chapter 2
Maternal Obesity During Pregnancy and Cardiometabolic Development in the Offspring

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Abstract Maternal obesity during pregnancy is a major public health problem worldwide. In Western countries, obesity prevalence rates in pregnant women are estimated to be as high as 30 %. In addition, it is estimated that in these countries approximately 40 % of women gain an excessive amount of gestational weight. An accumulating body of evidence strongly suggests a long-term impact of maternal obesity and excessive weight gain during pregnancy on adiposity and cardiometabolic related health outcomes in the offspring throughout the life course. Maternal obesity during pregnancy may lead to developmental adaptations in the offspring, predisposing to an increased risk of adverse cardiometabolic outcomes in later life. Thus far, it remains unclear whether these associations are explained by causal underlying mechanisms or reflect confounding by various family-based socio-demographic, nutritional, lifestyle-related and genetic characteristics. Further research to explore the causality, underlying mechanisms, and potential for prevention of cardiometabolic disease in future generations by reducing maternal obesity and excessive weight gain during pregnancy is needed.

Keywords Adverse pregnancy outcomes • Adult obesity • Cardiovascular risk factors • Childhood obesity • Excessive gestational weight gain • Maternal obesity • Paternal obesity • Pregnancy

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2.1 Introduction

Overweight, defined as a body mass index of 25.0–29.9 kg/m^2, and obesity, defined as a body mass index of 30.0 kg/m^2 or higher, are major public health problems worldwide. Over the past decades, the obesity prevalence has strongly increased in both high- and low-income countries. In 2014, the Word Health Organization estimated that more than 1.9 billion adults were overweight, of which over 600 million were obese [1]. The strong increase in obesity prevalence is also present among women of reproductive age. A large study combining data from nine states in the USA showed that from 1993 to 2003 there was a rise of 70 % in the rate of maternal obesity at the start of pregnancy [2]. Currently, obesity prevalence rates among women of reproductive age and at the start of pregnancy are estimated to be as high as 30 % in Western countries [3–5]. Next to prepregnancy obesity, it is estimated that in these countries approximately 40 % of women gain an excessive amount of gestational weight, based on the US Institute of Medicine (IOM) guidelines [6]. The IOM guidelines define optimal ranges of maternal weight gain during pregnancy according to a mother's prepregnancy body mass index and have been established based on evidence from observational studies that relate gestational weight gain to various maternal and offspring outcomes [6] (Table 2.1).

Both maternal prepregnancy obesity and excessive gestational weight gain may adversely affect fetal development through an excessive nutritional in utero environment. An accumulating body of evidence suggests that maternal obesity during pregnancy has persistent effects on various offspring outcomes [7, 8]. This chapter is focused on the associations of maternal obesity and excessive weight gain during pregnancy with cardiometabolic development in the offspring throughout the life course. Results from recent observational studies, with a specific focus on the Generation R Study, the causality, potential underlying mechanisms of the observed associations and challenges for future studies are discussed. This chapter is largely based on our previous reviews on this topic [7, 8].

Table 2.1 Institute of medicine criteria for gestational weight gain[a]

Prepregnancy body mass index	Recommended amount of total gestational weight gain in kg
Underweight (Body mass index < 18.5 kg/m^2)	12.5–18
Normal weight (Body mass index $\geq$ 18.5–24.9 kg/m^2)	11.5–16
Overweight (Body mass index $\geq$ 25.0–29.9 kg/m^2)	7–11.5
Obesity (Body mass index $\geq$ 30.0 kg/m^2)	5–9

[a]Recommended gestational weight gain guidelines according to women's prepregnancy body mass index. Adapted from the IOM criteria [6]

2.2 The Generation R Study

The Generation R Study is a multi-ethnic population-based prospective cohort study from fetal life until young adulthood in Rotterdam, The Netherlands [9]. The Generation R Study is designed to identify early environmental and genetic determinants of growth, development, and health in fetal life and childhood. All pregnant women living in the study area with a delivery date between April 2002 and January 2006 were eligible for enrolment in this study. Enrolment was aimed at early pregnancy, but was possible until the birth of the child. In total, 9778 mothers were enrolled in the study, of whom 8879 were included during pregnancy. During pregnancy, multiple assessments were planned in early pregnancy (<18 weeks of gestation), mid-pregnancy (18–25 weeks of gestation), and late pregnancy (≥25 weeks of gestation) and included parental physical examinations, fetal ultrasound examinations, and self-administered questionnaires. In the preschool period, from birth to 4 years of age, data collection was performed in all children by questionnaires and visits to the routine child health-care centers. All children were invited to a dedicated research center in the Erasmus MC—Sophia Children's Hospital to participate in detailed body composition and cardiovascular follow-up measurements at the age of 6 years. Measurements during this visit included anthropometrics, body composition by Dual Energy X-ray Absorptiometry and ultrasound, and measurements focused on cardiovascular development.

In the Generation R Study, the overall prevalence of maternal prepregnancy overweight and obesity is approximately 28 % [10]. There are large ethnic differences in maternal prepregnancy overweight and obesity prevalence. Among Dutch-origin women, the overweight and obesity prevalence is approximately 23 %. Higher prevalences of prepregnancy overweight and obesity are present among Cape Verdean-origin, Dutch Antillean-origin, Moroccan-origin, Surinamese-Creole-origin, and Turkish-origin women [4] (Fig. 2.1). The overall prevalence of excessive maternal gestational weight gain according to the IOM criteria within the Generation R Study is approximately 44 % [10]. As compared to Dutch-origin women, Moroccan-origin women and Surinamese-Hindustani-origin women tend to have a lower risk of excessive gestational weight gain [4].

2.3 Maternal Prepregnancy Body Mass Index

Many observational studies have shown that maternal prepregnancy obesity is an important risk factor for a variety of adverse fetal outcomes (Fig. 2.2). Based on these observational studies, multiple large meta-analysis have been performed. A meta-analysis focused on stillbirth among nine observational studies showed that the odds ratio of stillbirth was 2.07 [95 % Confidence Interval (CI): 1.59, 2.74] among obese pregnant women, as compared to normal-weight pregnant women [11]. In line with this meta-analysis, a large meta-analysis among 38 cohort studies
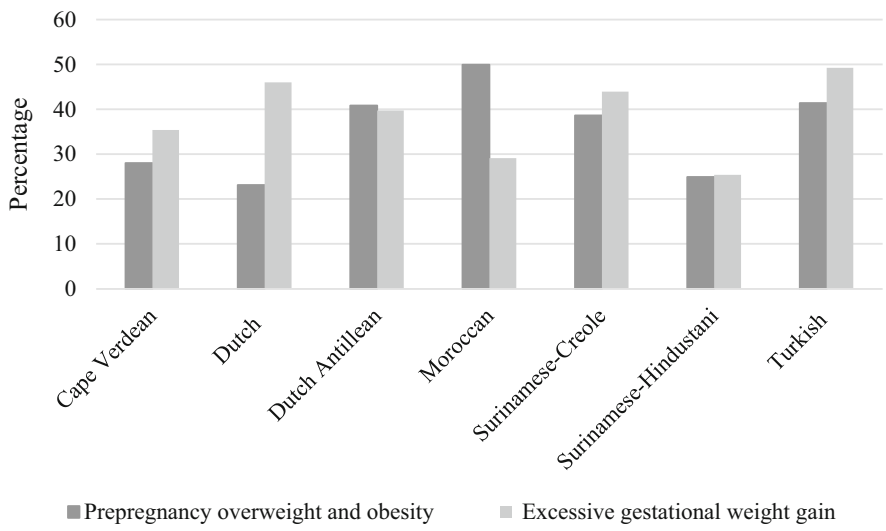
Fig. 2.1 Maternal obesity during pregnancy in the Generation R Study. Percentages of maternal prepregnancy overweight and obesity and excessive gestational weight gain among the largest ethnic groups within the Generation R Study [4]
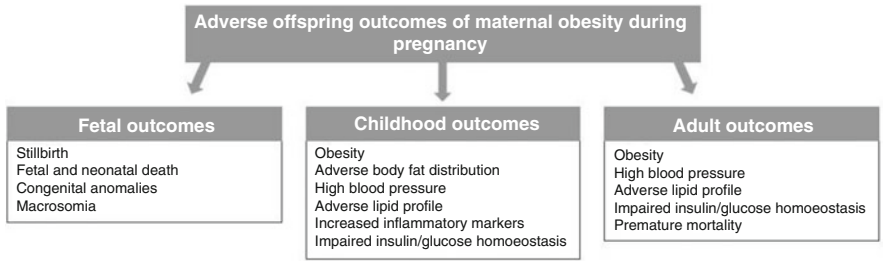

Fig. 2.2 Maternal obesity during pregnancy and adverse cardiometabolic outcomes in the offspring

in total with over 10,147 fetal deaths, 16,274 stillbirths, and 11,294 neonatal deaths showed that the risk of fetal death was 1.21 (95 % CI: 1.09, 1.35), the risk of stillbirth was 1.24 (95 % CI: 1.18, 1.30), and the risk of neonatal death was 1.15 (95 % CI: 1.07, 1.23) per 5-unit increase in maternal prepregnancy or early-pregnancy body mass index [12]. Maternal obesity was associated with an increased risk of a number of congenital anomalies in a meta-analysis among 18 observational studies, including neural tube defects, cardiovascular anomalies, cleft palate, hydrocephaly, and limb reduction anomalies [13]. A recent meta-analysis among 13 studies showed that, as compared to a normal maternal prepregnancy weight, maternal prepregnancy obesity was associated with a twofold higher risk of delivering a large size for gestational age infant [14].

Within the Generation R Study, we assessed the associations of maternal prepregnancy body mass index with fetal growth characteristics in each trimester of pregnancy. Maternal prepregnancy body mass index was not associated with first-trimester fetal crown-to-rump length [15]. Higher maternal prepregnancy body mass index was associated with a higher estimated fetal weight from mid-pregnancy onward, with stronger associations with advancing gestation [16]. Maternal prepregnancy obesity was also associated with an increased risk of cesarean delivery, preterm delivery, delivering a large size for gestational age infant, and a low APGAR score [10].

Maternal prepregnancy obesity is strongly associated with the risk of obesity in the offspring [7, 8]. A meta-analysis among four studies showed that maternal prepregnancy obesity was associated with a threefold higher risk of childhood obesity [17]. Also, multiple studies have shown that a higher maternal prepregnancy body mass index is associated with a higher body mass index in adolescent and adult offspring, independent from socio-demographic and lifestyle-related confounding factors [18–20]. A study among 1400 mothers and their adult offspring showed that offspring of mothers within the highest maternal prepregnancy body mass index quartile had a 5 kg/m^2 higher mean body mass index at the age of 32 years, as compared to offspring of mothers within the lowest maternal prepregnancy body mass index quartile [18].

The associations of maternal prepregnancy obesity with other cardiometabolic outcomes in the offspring have been studied less extensively [7, 8]. Within the Generation R Study, we showed that a higher maternal prepregnancy body mass index was associated with a higher offspring total body fat mass and android/gynoid fat mass ratio measured by Dual Energy X-ray Absorptiometry, and a higher abdominal subcutaneous and preperitoneal fat mass, a measure of visceral fat mass, at the age of 6 years [21]. Also, a higher maternal prepregnancy body mass index was associated with a higher childhood systolic blood pressure and insulin levels and lower HDL cholesterol levels. As compared to children from normal-weight mothers, children from obese mothers had an increased risk of clustering of cardiometabolic risk factors [OR 3.00 (95 % CI: 2.09, 4.34)], a measure of a metabolic syndrome like phenotype. The associations of maternal prepregnancy body mass index with childhood cardiometabolic risk factors were largely mediated by childhood concurrent body mass index [21]. A study among 1090 mother–child pairs participating in a pre-birth cohort in the USA showed that a higher maternal prepregnancy body mass index was also associated with higher mid-childhood leptin, high sensitivity C-reactive protein and interleukin-6 levels, and lower adiponectin levels [22].

Similar associations have been reported in adolescence and adulthood [7, 8]. A study among 4452 mothers and their adolescent offspring in Brazil showed that a higher maternal prepregnancy body mass index was associated with a higher adolescent systolic and diastolic blood pressure in boys and girls [23]. Among 1392 Australian mothers and their adolescent offspring, it was shown that a higher maternal prepregnancy body mass index was associated with a higher adolescent waist circumference, waist to hip ratio, systolic blood pressure, insulin, glucose,

and HOMA-IR levels at the age of 17 years [24]. A study among 1400 mother–offspring pairs in Jerusalem showed that maternal prepregnancy body mass index was positively associated with waist circumference, systolic and diastolic blood pressure, insulin, and triglycerides and negatively with HDL cholesterol in the offspring at the age of 32 years [18]. In line with findings from studies focused on childhood outcomes, these studies focused on adolescent and adult outcomes showed that additional adjustment for offspring concurrent body mass index attenuated the associations of maternal prepregnancy body mass index with offspring cardiometabolic risk factors. A study using birth records from 37,709 participants showed that a higher maternal body mass index at the first antenatal visit was associated with a higher risk of premature all-cause mortality and hospital admissions for cardiovascular events in adult offspring, with a hazard of all-cause mortality in offspring of obese mothers of 1.35 (95 % CI: 1.17, 1.55), as compared to offspring from mothers with a normal body mass index at the first antenatal visit [25]. These associations were not explained by adjustment for maternal age at delivery, socioeconomic status, sex of offspring, current age, birth weight, gestational age at delivery, and gestational age at measurement of maternal body mass index, but no information on concurrent body mass index of adult offspring was available [25].

Thus, maternal prepregnancy obesity is associated with increased risks of adverse fetal outcomes, adiposity, and adverse cardiometabolic development in childhood, adolescence, and adulthood and premature death in adulthood. The associations of maternal prepregnancy body mass index with offspring cardiometabolic risk factors seem to be largely explained by offspring body mass index.

2.4   Maternal Gestational Weight Gain

Next to maternal prepregnancy body mass index, excessive maternal weight gain during pregnancy may be an independent risk factor of adverse fetal development and cardiometabolic development from childhood onwards (Fig. 2.2) [7, 8]. Different measures of maternal weight gain during pregnancy have been studied. Most studies have focused on the associations of excessive maternal weight gain during pregnancy defined according to the IOM criteria. However, from a research perspective, the IOM criteria for excessive gestational weight gain have important limitations [26]. As the IOM criteria for excessive gestational weight gain combine prepregnancy body mass index and gestational weight gain, it is not possible to study the distinct effects of maternal prepregnancy body mass index and gestational weight gain on offspring outcomes [26]. In addition, it is not possible to identify critical periods of maternal weight gain for offspring outcomes. Recently, more studies have therefore also focused on more detailed measures of maternal weight gain during pregnancy.

Excessive maternal gestational weight gain is associated with several adverse fetal outcomes, but associations seem to be weaker and less consistent as compared to the associations of maternal prepregnancy body mass index [7, 8]. Excessive gestational weight gain is most consistently associated with an increased risk of delivering a large size for gestational age infant. A meta-analysis among 15 cohort and case–control studies showed that excessive gestational weight gain based on the IOM criteria was associated with a 2.35 (95 % CI: 1.95, 2.85) higher risk of macrosomia [27]. Thus far, excessive gestational weight gain seems not to be associated with fetal death or stillbirth [28, 29]. A meta-analysis among 24 cohort studies and 14 case–control studies showed that not a high total gestational weight gain but a high weekly gestational weight gain was associated with an increased risk of preterm birth [30]. A study among 20,465 nondiabetic, term, singleton-born infants showed that excessive gestational weight gain according to the IOM criteria was associated with adverse neonatal outcomes, such as a low 5-min APGAR score and neonatal hypoglycemia [31]. Within the Generation R Study, we observed that excessive maternal weight gain during pregnancy according to the IOM criteria was associated with a higher risk of cesarean delivery and large size for gestational age at birth, but a lower risk of preterm birth and small size for gestational age at birth [10]. When we assessed the trimester-specific effects of maternal weight gain during pregnancy, we observed that especially higher second- and third-trimester maternal weight gain was associated with an increased risk of delivering a large size for gestational age infant [10].

A meta-analysis among 12 studies showed that as compared to a recommended amount of gestational weight gain according to the IOM criteria, excessive gestational weight gain was associated with a 33 % increased risk of childhood obesity [32]. A systematic review among seven studies also assessed the associations of total gestational weight gain with the risk of childhood obesity and showed that an additional kilogram increase in total gestational weight gain was associated with a higher child's BMI z-score of 0.006–0.06 units and increased the risk of childhood overweight or obesity by 1–23 % after adjustment for potential confounding factors [33]. The associations of excessive gestational weight gain or total gestational weight gain with more detailed childhood fat mass measures, blood pressure, lipid levels, insulin resistance, and inflammatory markers are less consistent and, if present, seem to be largely mediated by childhood body mass index [22, 34–40].

Similarly, increased maternal weight gain during pregnancy has been associated with higher offspring adiposity levels and cardiovascular risk factors in adulthood [18, 20, 41–43]. A study among 1540 Danish mothers and their offspring showed that per kilogram increase in maternal gestational weight gain the odds ratio for obesity at the age of 42 years was 1.08 (95 % CI: 1.03–1.14) [20]. This association was only partly explained by offspring birth weight and body mass index up to 14 years of age [20]. A study among 2432 Australians showed that higher maternal gestational weight gain was independent from maternal prepregnancy body mass index, associated with a higher body mass index, and tended to be associated with a higher systolic blood pressure in the offspring at the age of 21 years [43]. A study among 1400 mother–offspring pairs in Jerusalem showed higher maternal

gestational weight gain was only associated with increased adiposity levels in the offspring aged 32 years, but not with other cardiovascular risk factor [18]. Another study among 308 Danish mother– offspring pairs, which assessed the associations of maternal weight gain among normal-weight women, showed that a higher maternal weight gain was associated with higher insulin levels and leptin levels among male offspring only [41].

Several studies aimed to identify critical periods of maternal weight gain during pregnancy for childhood and adolescent outcomes [7, 8]. Within the Generation R Study, we showed among 5908 mother–offspring pairs that independent from maternal prepregnancy weight and weight gain in later pregnancy, early-pregnancy weight gain was associated with higher adiposity levels and an adverse cardiometabolic profile at the age of 6 years [39]. In line with our findings, a study performed among 5154 UK mother–offspring pairs showed that gestational weight gain in the first 14 weeks of pregnancy was positively associated with offspring body mass index, waist circumference, and fat mass at the age of 9 years [35]. A study among 977 mother–child pairs from Greece showed that maternal first-trimester weight gain was associated with an increased risk of childhood obesity and a higher childhood diastolic blood pressure from 2 to 4 years [44]. A Finnish study among 6637 mothers and their adolescent offspring showed that maternal weight gain of >7 kg in the first 20 weeks of gestation was associated with the risk of offspring overweight and abdominal adiposity at the age of 16 years [45]. A study among 1392 Australian mothers and their adolescent offspring showed that higher maternal weight gain rate in early but not in mid-pregnancy was associated with greater adiposity levels and an increased risk of being in the high-metabolic risk cluster, a proxy measure of the metabolic syndrome at 17 years [24]. These studies suggest that especially maternal weight gain during early pregnancy, when maternal fat accumulation forms a relatively large component of gestational weight gain, may be a critical period for an adverse cardiovascular risk profile in the offspring.

Thus, next to maternal prepregnancy obesity, excessive maternal weight gain during pregnancy may also lead to increased risks of adverse fetal outcomes, adiposity, and adverse cardiovascular risk factors in childhood, adolescence, and adulthood. The adverse effects of maternal weight gain during pregnancy may depend upon the timing of gestational weight gain. Overall, maternal prepregnancy obesity appears to be more strongly associated with adverse offspring outcomes than excessive gestational weight gain. Importantly, both the associations of maternal body mass index and gestational weight gain with offspring outcomes seem not to be only restricted to maternal obesity or excessive gestational weight gain, but are present across the full-range of maternal body mass index and gestational weight gain [7, 8].

2.5 Causality of the Observed Associations

Despite the large number of observational studies reporting these associations, limitations in these studies need to be considered. The most important limitation of these observational studies is confounding of the observed associations [7, 8]. Various family-based socio-demographic, nutritional, lifestyle-related, and genetic characteristics may explain the observed associations of maternal prepregnancy body mass index and gestational weight gain with adverse offspring health outcomes [7, 8]. Multiple more sophisticated study designs can be used to obtain further insight into the role of confounding in the observed associations, including sibling comparison studies, maternal and paternal offspring comparison analyses, Mendelian randomization studies, and randomized controlled trial analyses, as we described previously [7, 8].

2.5.1 Sibling Comparison Studies

The main advantage of sibling comparison studies is their ability to better control for potential confounding factors, such as environmental characteristics as well as maternal genotype, shared within families [46]. A sibling comparison study focused on severe maternal prepregnancy obesity showed among children from mothers who had high levels of prepregnancy weight loss due to biliopancreatic bypass surgery that the risk of overweight and obesity and adverse cardiometabolic risk factors was higher in children born to mothers before surgery than those born to mothers after surgery [47, 48]. A sibling comparison study among 513,501 mothers and their 1,164,750 children showed that children born to mothers who gained more than 24 kg during pregnancy were approximately 148 g (95 % CI: 141.7, 156.0) heavier at birth than were children born to mothers who gained 8–10 kg [49]. A sibling comparison study among 42,133 women who had more than one singleton pregnancy and their 91,045 offspring showed that higher maternal total gestational weight gain was associated with a higher body mass index in childhood, where every additional kilogram of gestational weight gain increased childhood BMI by 0.0220 kg/m^2 (95 % CI 0.0134–0.0306) [50]. This association was only partly mediated by offspring birth weight. A study using a sibling comparison design among 280,866 singleton-born Swedish men showed that a higher maternal body mass index in early pregnancy was not associated with higher offspring body mass index at the age of 18 years within siblings, but only in the whole cohort and between non-siblings [51]. This suggests that the association may be explained by confounding environmental characteristics [51]. However, among the same study population it was also shown that among overweight and obese mothers, higher total gestational weight gain was associated with higher offspring body mass index at the age of 18 years among siblings, which suggests a possible intrauterine effect for gestational weight gain [52]. Findings from these sibling comparison studies

suggest that especially gestational weight gain may affect offspring outcomes through direct intrauterine mechanisms. An important limitation of sibling comparison studies is that next to the major exposures of interest, maternal prepregnancy body mass index and gestational weight gain, also other lifestyle-related characteristics may differ between pregnancies [7, 8].

2.5.2 Parent–Offspring Comparison Studies

As an aid to further disentangle underlying mechanisms, the strength of associations of maternal and paternal body mass index with offspring outcomes can be assessed [53]. Stronger associations for maternal body mass index suggest direct intrauterine mechanisms, whereas similar or stronger associations for paternal body mass index suggest a role for shared family-based, lifestyle-related characteristics or genetic factors [54]. Multiple studies compared the associations of maternal and paternal body mass index with childhood body mass index and have shown conflicting results [55]. However, studies examining these associations with more detailed childhood fat mass measures have shown that maternal prepregnancy body mass index tends to be more strongly associated with childhood total fat mass than paternal body mass index [21, 56, 57]. Within the Generation R Study, we observed that maternal prepregnancy body mass index was more strongly associated with childhood body mass index, total body fat mass, android–gynoid fat mass ratio, and clustering of cardiometabolic risk factors than paternal prepregnancy body mass index [21]. These findings suggest that some of the effects of maternal prepregnancy obesity on offspring outcomes may be through direct intrauterine mechanisms [7, 8].

2.5.3 Mendelian Randomization Studies

Mendelian randomization studies are studies in which genetic variants, known to be robustly associated with the exposure of interest and not affected by confounding, are used as an instrumental variable for a specific exposure [58]. Associations of these genetic variants with the outcomes of interest support causality for these associations. A study among 4091 mother–offspring pairs showed no association of maternal FTO with childhood fat mass at the age of 9 years [57]. Thus far, no other Mendelian randomization studies on these specific associations have been performed.

2.5.4   Randomized Controlled Trials

Randomized controlled trials are considered as the golden standard to assess causality. Previous randomized controlled trials have focused on influencing determinants of maternal obesity and excessive weight gain during pregnancy, such as dietary factors and physical activity levels, since directly randomized studies are difficult to perform with maternal prepregnancy obesity and excessive gestational weight gain as major exposures of interest [59]. A meta-analysis of multiple randomized controlled trials showed that dietary and physical activity interventions aimed at reducing maternal weight gain during pregnancy may lead to small reductions in the amount of gestational weight gain and to a slightly lower risk of adverse pregnancy outcomes [59]. In this meta-analysis, dietary interventions appeared to be more effective than physical activity-related interventions [59]. A recent Cochrane review also suggested that interventions during pregnancy focused on diet or exercise, or combined, can reduce the risk of excessive gestational weight gain [60]. However, whether these interventions also have a beneficial effect on long-term offspring health outcomes remains unclear. A small randomized controlled trial among 254 mothers and their children, which provided both dietary advice and exercise during pregnancy to obese women, observed no difference in body mass index or metabolic risk factors in infant offspring, when compared to the control group and an external reference group of normal-weight women [61].

Taken together, results from these studies specifically designed to explore the causality for the associations of maternal prepregnancy body mass index and gestational weight gain with offspring outcomes remain inconclusive [7, 8].

2.6   Underlying Mechanisms

The mechanisms underlying the associations of maternal prepregnancy obesity or excessive gestational weight gain with cardiometabolic disease in the offspring remain unclear. The fetal overnutrition hypothesis suggests that in obese mothers and mothers with high levels of gestational weight gain an increased placental transfer of nutrients to the developing fetus may subsequently affect fetal development, fetal fat deposition, and the development of the hypothalamic–endocrine system that controls appetite and energy metabolism [26, 62, 63]. These adaptations may predispose individuals to a greater risk of adverse cardiometabolic outcomes in later life. Figure 2.3 shows potential mechanisms that might be involved in the associations of higher maternal prepregnancy body mass index and gestational weight gain with adverse cardiometabolic development in the offspring [8]. As described previously, the following maternal exposures and underlying mechanisms may have an important role [8].
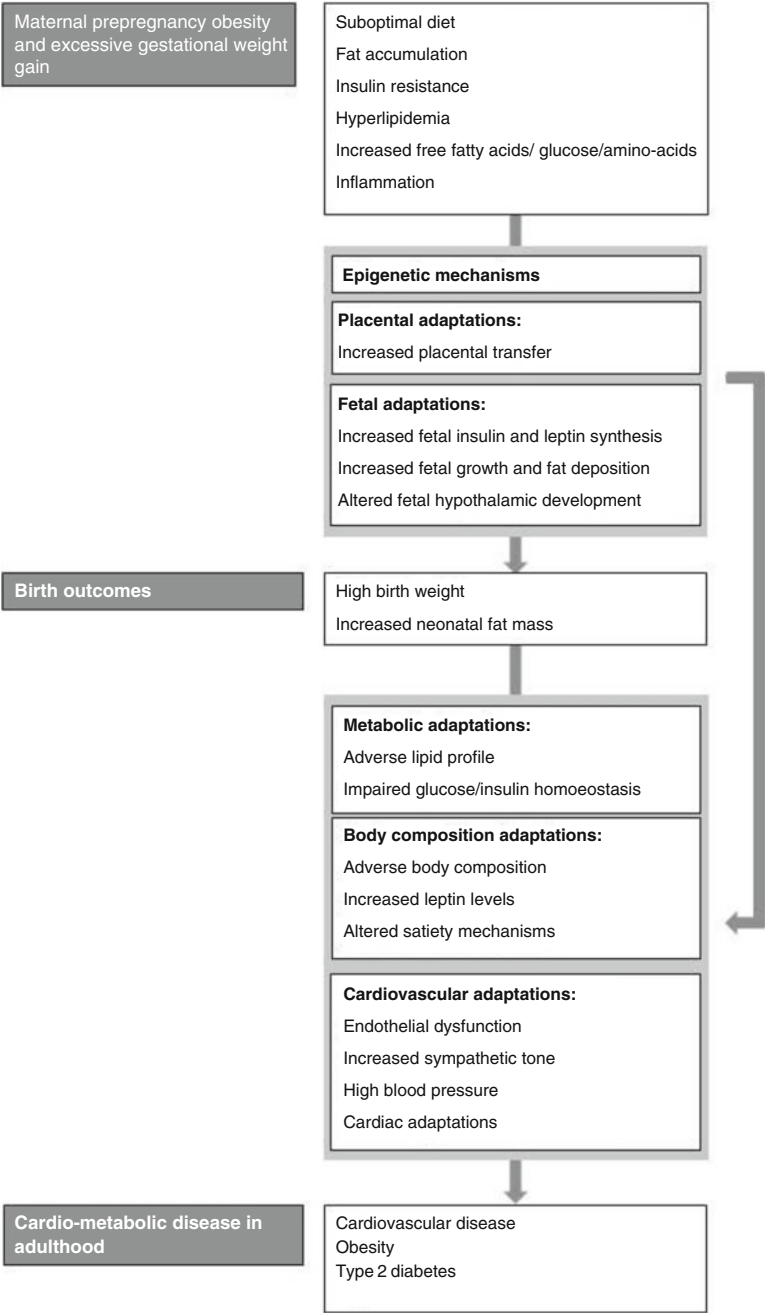
Maternal prepregnancy obesity and excessive gestational weight gain	Suboptimal diet
	Fat accumulation
	Insulin resistance
	Hyperlipidemia
	Increased free fatty acids/ glucose/amino-acids
	Inflammation

Epigenetic mechanisms

Placental adaptations:

Increased placental transfer

Fetal adaptations:

Increased fetal insulin and leptin synthesis

Increased fetal growth and fat deposition

Altered fetal hypothalamic development

Birth outcomes	High birth weight
	Increased neonatal fat mass

Metabolic adaptations:

Adverse lipid profile

Impaired glucose/insulin homoeostasis

Body composition adaptations:

Adverse body composition

Increased leptin levels

Altered satiety mechanisms

Cardiovascular adaptations:

Endothelial dysfunction

Increased sympathetic tone

High blood pressure

Cardiac adaptations

Cardio-metabolic disease in adulthood	Cardiovascular disease
	Obesity
	Type 2 diabetes

Fig. 2.3 Maternal obesity during pregnancy and offspring developmental adaptations. Conceptual model for potential underlying mechanisms for the associations of maternal obesity during pregnancy with adverse cardio-metabolic health outcomes in offspring. Adapted from [8]

2.6.1 Maternal Exposures

Both maternal prepregnancy obesity and excessive gestational weight gain are complex traits [8]. Maternal prepregnancy obesity not only reflects maternal fat accumulation, but also other maternal characteristics, such as maternal nutritional status, insulin and glucose metabolism, and low-grade systemic inflammation. Similarly, maternal weight gain during pregnancy reflects maternal fat accumulation, but also maternal and amniotic fluid expansion and growth of the fetus, placenta, and uterus [6]. Multiple studies aimed to study the associations of more detailed exposures related to maternal prepregnancy obesity and excessive gestational weight gain with various offspring outcomes [8].

Maternal fat accumulation during pregnancy is important for fetal nutrient supply and fetal development [64]. However, during pregnancy, fat accumulation predominantly occurs centrally [64]. Central fat accumulation is well known to be associated with adverse cardiometabolic outcomes and appears to have similar adverse consequences in pregnant women [65]. These metabolic disturbances may involve insulin resistance and dyslipidemia, which leads to higher maternal circulating levels of free fatty acids, amino acids, and glucose, which affect placental and fetal development [64]. Multiple observational studies, including studies using a sibling comparison design, have shown that gestational diabetes, glycosuria, and higher maternal fasting glucose levels during pregnancy are associated with higher weight and c-peptide levels at birth and higher body mass index, fat mass level, fasting glucose and insulin levels, and the risk of type 2 diabetes in later life [51, 66–71]. Small observational studies have also shown that higher maternal triglyceride and amino acid levels are associated with a higher birth weight and neonatal fat mass [72–75]. Thus, maternal fat accumulation and metabolic factors during pregnancy may have persistent effects on offspring cardiometabolic development [8].

Maternal obesity during pregnancy may be an indicator of a poor quality maternal diet [8]. A Western dietary pattern and macronutrients and micronutrients intake related to a Western diet have been suggested to influence offspring fat deposition, adipocyte function, pancreatic function, and food preference [62, 76]. A maternal diet during pregnancy which is high in saturated fat and sugar intake is associated with an increased risk of obesity in the offspring [77]. Also, a maternal diet with low *Omega-3* and high *Omega-6* fatty acids intake seems to be associated with an increased risk of childhood obesity [78–80]. A study among 906 UK mother–child pairs showed that higher maternal dietary glycemic index and glycemic load in early pregnancy, but not later in pregnancy, were associated with higher fat mass in children at the age of 4 and 6 years [81]. A study among approximately 3000 parents and their children showed that maternal protein, fat, and carbohydrate dietary intake during pregnancy, but not paternal dietary intake, was associated with child's dietary intake of the same macronutrients [82]. The associations of maternal dietary intake during pregnancy with child's dietary intake were also stronger than the associations of maternal postnatal dietary intake, which suggest

that in utero mechanisms may play a role in the programming of offspring appetite [82]. Altogether, these studies suggest that various measures reflecting a suboptimal dietary status in pregnant women are associated with adverse cardiovascular and metabolic outcomes in offspring [8].

Obesity is associated with low-grade systemic inflammation and oxidative stress, also during pregnancy [83–85]. Additionally, pregnancy itself leads to a state of mild maternal systemic inflammation, which may interact with obesity-mediated inflammatory mechanisms [86–89]. Thus far, it has been shown that maternal inflammatory markers during pregnancy correlate with fetal growth and neonatal fat mass [90, 91], but the effects at older ages are less clear and remain to be further explored [92].

2.6.2   Programming Mechanisms

Both maternal prepregnancy obesity and excessive gestational weight gain as well as the correlated maternal exposures may lead to programming effects in the offspring through several pathways [8].

Epigenetic mechanisms, which involve modifications due to early environmental influences to DNA and its associated proteins that regulate gene activity, are likely to play a key role in developmental programming of adverse cardiometabolic outcomes [93, 94]. Thus far, animal studies provide support for epigenetic modifications due to maternal obesity or a high-fat diet, but this has not been explored in large human studies [93]. Small studies among pregnant women showed that maternal obesity and impaired maternal glucose tolerance induced epigenetic changes of placental genes [88, 95–97]. A human study among 88 mother–child pairs suggested that only maternal weight gain in early pregnancy might be associated with epigenetic modifications in offspring cord blood [98]. Epigenetic modifications together with other mechanisms may thus be involved in adiposity and cardiovascular and metabolic developmental adaptations [8].

Offspring from mothers with prepregnancy obesity or excessive gestational weight gain are at increased risk of being born large for their gestational age, which itself is associated with an increased risk of obesity in later life [99]. The associations of maternal obesity during pregnancy with the risk of obesity in childhood and adulthood may thus be explained by tracking of body size and fatness throughout the life course [8]. However, many observational studies have shown that additional adjustment for birth weight does not explain the observed associations [7, 8]. The lack of effect of adjustment for birth weight may partly be explained by birth weight not accurately reflecting neonatal fat mass, but might also suggest that other mechanisms are involved in these associations [62]. Animal studies have suggested that maternal obesity during pregnancy may affect both offspring adipocyte morphology and metabolism, which may influence the development of obesity and insulin resistance in the offspring [8, 63]. Next to altered growth and adipocyte function, altered appetite control may be a key factor in

developmental programming of obesity [8]. A maternal hypercaloric diet during pregnancy and overfeeding in the fetal and early postnatal period may lead to hyperphagia and altered satiety mechanisms through adverse programming of the hypothalamus by high fetal and infant leptin and insulin levels [62, 100].

The associations of maternal prepregnancy body mass index and gestational weight gain with adverse cardiovascular and metabolic outcomes in the offspring appear to be largely mediated through offspring adiposity [8]. However, direct cardiovascular and metabolic programming effects of maternal obesity during pregnancy may also be present [63]. Thus far, mainly animal studies have shown that maternal obesity, a maternal high-fat diet, and increased maternal glucose transport during pregnancy are associated with offspring high blood pressure, endothelial dysfunction, increased aortic stiffness, cardiac hypertrophy, impaired glucose and insulin homeostasis, and measures related to non-alcoholic fatty liver disease [8, 63, 100, 101].

Thus, multiple mechanisms may be involved in the intrauterine pathways leading from maternal obesity and excessive weight gain during pregnancy to long-term adverse offspring health outcomes [8]. These underlying mechanisms have mainly been studied in animal models and remain to be further explored in large human studies.

2.7 Challenges for Future Epidemiological Research

Current evidence from epidemiological studies suggests that maternal obesity and excessive weight gain during pregnancy have important adverse consequences on cardiometabolic development from fetal life onwards, leading to disease in later life [7, 8]. However, there remain important issues to be addressed [7, 8]. These include examining the extent of causality of the observed associations, the underlying exposures and their critical periods, the developmental adaptations, and the potential for development of preventive strategies (Table 2.2) [7, 8].

First, despite extensive adjustment for potential confounding factors in these observational studies, residual confounding may still be an issue [7, 8]. The causality of the observed associations needs to be further addressed. For this purpose,

Table 2.2 Key points for future research[a]

Observational studies using sophisticated study designs to obtain further insight into the causality of the observed associations
Detailed maternal exposures and offspring outcomes measurements to obtain further insight into the specific exposures and their critical periods, and the underlying mechanisms of the observed associations
Long-term follow-up of participants in trials focused on reducing maternal weight throughout pregnancy to assess causality of the observed associations and the effectiveness of maternal lifestyle interventions during pregnancy for improving long-term health outcomes of offspring

[a]Adapted from [8]

large observational studies that are able to conduct sophisticated analyses, such as sibling comparison analyses, parent–offspring comparison analyses, and Mendelian randomization analyses, are needed. In addition, meta-analyses among large numbers of observational studies will provide further insight into the strength, consistency, and independency of these associations. Long-term follow-up of mothers and their children participating in randomized controlled trials focused on reducing maternal weight throughout pregnancy will also provide further insight into the causality of the associations [7, 8].

Second, the mechanisms underlying the observed associations of maternal prepregnancy obesity and excessive gestational weight gain with offspring health outcomes remain to be further explored [7, 8]. Animal studies have identified a number of pathways that may be involved in these associations, but these pathways remain largely unexplored in humans. Maternal prepregnancy obesity and excessive gestational weight gain are complex traits, which reflect multiple biological and lifestyle-related components, which complicates identification of potential underlying pathways [7, 8]. Future studies with more detailed assessments of the maternal exposures and offspring outcomes throughout the life course could provide further insight into potential underlying mechanisms. To obtain further insight into the different maternal components associated with offspring outcomes and their critical periods, detailed repeated measurements of maternal weight and body composition, nutritional status, metabolic measures, inflammatory measures, and pregnancy-related hemodynamic adaptations are needed. Since early pregnancy appears to be a critical period for offspring outcomes, studies are needed with detailed maternal measurements from early pregnancy onward to already assess their influence on placental and embryonic growth and development. For the offspring outcomes, more detailed measurements of fetal and postnatal growth, body composition, and cardiometabolic factors, such as cardiac structures, endothelial function, lipid spectrums, and glucose responses, might also lead to further insight into the underlying growth, vascular, and metabolic mechanisms present in the observed associations. Long-term follow-up of the offspring in observational studies is needed to assess the influence of maternal prepregnancy obesity and excessive gestational weight gain on cardiovascular and metabolic development throughout the life course [7, 8].

Third, further research is needed focused on prevention of adverse health outcomes in offspring through optimizing maternal prepregnancy body mass index, gestational weight gain, and dietary intake during pregnancy [7, 8]. The optimal amounts of maternal weight gain for short-term and long-term maternal and offspring health outcomes need to be examined to improve the IOM recommendations for gestational weight gain [7, 8]. Identification of specific maternal dietary components associated with offspring health outcomes will aid in the improvement of maternal dietary recommendations during pregnancy [7, 8]. Long-term follow-up of mothers and their children participating in randomized controlled trials focused on improving maternal diet and reducing maternal weight throughout pregnancy will provide insight into the effectiveness of these maternal lifestyle interventions during pregnancy for improving long-term health of offspring [7, 8].

2.8   Conclusions

Based on current evidence from observational studies, maternal prepregnancy obesity and excessive gestational weight gain seem to be risk factors for an adverse in utero environment and long-term adverse cardiometabolic outcomes in the offspring. Well-designed studies are needed to identify the extent of causality of the observed associations, the underlying exposures and their critical periods, the developmental adaptations, and the potential for development of preventive strategies to improve long-term health outcomes of offspring.

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