Update on Prepregnancy Maternal Obesity: Birth Defects and Childhood Outcomes

Noha Iessa1,2 Anick Bérard1,2

1 Faculty of Pharmacy, University of Montreal, Montreal, Québec, Canada
2 Research Center, CHU Sainte-Justine, Montreal, Québec, Canada

J Pediatr Genet 2015;4:71–83.

Abstract
Keywords
► obesity
► body mass index
► pregnancy
► major congenital malformations

Obesity is a growing global health epidemic. It is estimated that more than 20% of pregnancies are complicated by obesity. Prepregnancy obesity has been associated with birth defects such as neural tube defects, macrosomia, fetal death, and long-term effects such as asthma on the offspring. We provide a summary of the most recent studies and meta-analyses on obesity and birth outcome. Possible mechanisms of actions are explored and recommendations for further research are highlighted.

Introduction

Obesity is a growing global health epidemic affecting adults and children in both developed and developing countries.1–4 One in five women in the United Kingdom and approximately 36% of adults in the United States are classified as obese.5 Prevalence of obesity in pregnancy has been rising since 1993, and it was estimated that 50% of childbearing women in the United Kingdom were overweight or obese in 2006.6

It is well known that obesity is a major risk factor in adults for noncommunicable diseases such as diabetes, cardiovascular diseases, musculoskeletal disorders, and some cancers, resulting in premature death and disability. At least 2.8 million people die every year as a result of being overweight or obese.7 Obesity also affects pregnancy and more than 20% of pregnancies are complicated by obesity.5–8 Maternal obesity has been associated with increased rates of preeclampsia, gestational diabetes and need for operative delivery,9–11 and increased risks of adverse reproductive outcomes affecting fetal development, the neonatal period, and overall childhood development.12,13

Obesity is a multifactorial condition in which environmental, biological and genetic factors play an essential role. It represents a state of altered hormonal and inflammatory activity associated with fatty tissue.14 A woman may be obese prior to pregnancy or become obese during pregnancy due to excessive gestational weight gain. These are both independent factors, and we focus on prepregnancy obesity in this review. The World Health Organization defines obesity as abnormal or excessive fat accumulation that may impair health. Body mass index (BMI) is a measure calculated by dividing a person’s weight (kg) by the square of the height (m²).7 A BMI greater than or equal to 30 is considered obese, whereas a BMI greater than or equal to 25 is overweight. Maternal obesity is defined as a BMI of 30 kg/m² or greater, and being overweight during pregnancy (maternal overweight) is defined as a BMI between 25 and 29.9 kg/m². Maternal obesity can be further divided into class I (BMI = 30–34.9), class II (BMI = 35–39.9), and class III (BMI ≥40).15

Earlier publications have reviewed the association between maternal obesity and comorbid conditions, such as hypertensive disease or diabetes, with adverse pregnancy outcomes and fetal malformations.16–18 More recent studies have added to existing knowledge, and associations between other outcomes in offspring such as neurodevelopmental disorders and asthma are emerging. In this paper, we review the metabolic differences in obese and nonobese women, and provide an update of evidence on fetal development and neurodevelopmental outcomes in offspring of maternal obese women.
Metabolic Changes and Obesity in Pregnancy

Intrauterine Environment and “Fetal Programming”

The intrauterine environment in pregnancy is thought to play a major role in physiologic alterations in the offspring. It is hypothesized that the intrauterine environment can “program” later development of obesity, hypertension metabolic syndrome, and neurodevelopmental outcomes in the offspring. This is known as the fetal programming hypothesis.\(^{19,20}\) The intrauterine environment is affected by altered nutritional experiences and chemical changes during pregnancy.

Obese women tend to have increased levels of insulin, cytokines, protein hormones, and leptin, regardless of the presence of comorbidities such as diabetes.\(^{10,21}\) In addition, obese women have higher insulin resistance and are at increased risk of metabolic syndrome-like disorders during pregnancy, such as hypertension, hyperlipidemia, glucose intolerance, and coagulation disorders.\(^{22}\)

High levels of proinflammatory cytokines such as tumor necrosis factor-\(\alpha\), interleukin, monocyte chemotactic protein-1, and procoagulant proteins are found in obese nonpregnant individuals.\(^{23,24}\) It is thought that obesity increases baseline proinflammatory mediators, which increases the risk of maternal diseases (preeclampsia) and neonatal complications.\(^{25–34}\)

Fetal Development

The hormonal and chemical changes that occur in pregnancy can affect various stages in fetal development and maternal health. Insulin and leptin function as growth factors and can elevate progesterone concentrations. This can alter transcriptional activity during oocyte growth and impair mechanisms of RNA translation and degradation during oocyte maturation. This leads to reduced oocyte quality and poor embryogenesis.\(^{35}\) Hence, the environmental messages are translated to the structure and function of the developing fetus leaving a permanent mark. Changes in gene-environment interactions start in the periconception period and continue into later life producing a phenotype, which continues to evolve.\(^{36}\)

Insulin and leptin are involved in the development of the central nervous system in early stages of pregnancy. Alterations in levels of these hormones have been shown to induce changes in brain development in animal models.\(^{37,38}\) It is thought that in humans, alteration in the developmental program of specific brain cell networks could lead to conditions such as metabolic syndrome and neurologic disorders in the offspring at later ages.\(^{39}\)

Obesity and Other Maternal Metabolic Phenotypes

The maternal phenotype may have a direct impact on the infant’s phenotype, in particular when combined with hormonal tensions caused by over or under placental nutrition.\(^{40}\) Maternal metabolic phenotypes include obesity, pregestational diabetes (types 1 and 2), gestational diabetes, and hypertension.

Metabolic abnormalities are not uniform in all obese persons, and an individual can be metabolically healthy but obese; or have metabolically disturbances but have a normal body weight. The standard measure of obesity is the BMI, which is calculated using overall body weight rather than fat percentage. In the average individual, excess weight is primarily due to increased adipose tissue. Adipose tissue is composed of subcutaneous and visceral depots. Subcutaneous tissue forms a continuous layer beneath the skin and is not confined to specific areas. Visceral adipose tissue is confined to the intra-abdominal area, and can be measured with indicators such as waist circumference (applicable to women only during early pregnancy or at preconception), or directly by imaging techniques such as computed tomography.\(^{31,42}\) Obese individuals can have high or low visceral adiposity phenotypes. Viscerally obese patients represent a subgroup of obese individuals who are at greater risk of metabolic abnormalities.\(^{43,44}\) This includes insulin resistance leading to overproduction of free fatty acids, and increased secretion of triglyceride rich lipoproteins.\(^{42}\) Viscerally obese individuals have also been shown to have impaired fibrinolysis, increased susceptibility to thrombosis, and to be in a chronic inflammatory state.\(^{42}\) Hence, mothers with visceral obesity expose their fetuses to an altered metabolic intrauterine environment, which increases the risk of obesity and other metabolic disorders later in the life of the offspring (►Table 1). This effect has the potential to play a role in future generations, as seen with type 2 diabetes in Pima Indians over the last three decades.\(^{40}\) The incidence of type 2 diabetes has increased two- to fourfold in this population after a transmission cycle of metabolic phenotype, due to a secular increase in maternal type 2 diabetes and subsequent childhood obesity.\(^{40}\) Further research is needed to assess the long-term effects of overnutrition on the offspring—specifically focusing on the effect of an extra increment of maternal adiposity. In addition, further understanding of the intrauterine mechanisms related to the transmission of obesity through generations is needed by conducting long-term follow-up studies.

If maternal undernutrition occurs early in intrauterine life (first and second trimesters), the offspring are also more likely to be obese in adult life.\(^{45}\) It has been suggested that undernutrition during this time can lead to underdevelopment of the hypothalamic appetite centers leading to overeating and obesity in postnatal life.\(^{46}\)

All three types of maternal diabetes (type 1, type 2, and gestational) are associated with an increased fetal and infant growth rate (►Table 1). Gestational diabetes usually occurs in the later stages of pregnancy. Gestational diabetes is thought to induce hyperglycemia in the fetus (in later stages of pregnancy) and causes dysfunction of the pancreas, chronic hyperinsulinemia, and macrosomia.\(^{47}\) Type 2 diabetes is associated with an increase in obesity and type 2 diabetes in the offspring. This effect is thought to occur in early pregnancy due to alterations in the intrauterine environment.\(^{48}\)

Interventions to prevent effects of obesity and diabetes on the offspring should be targeted to females throughout their life span, particularly in the preconception time period, as pregnancy itself may be too late to intervene.
Table 1 Maternal metabolic phenotypes and potential risks to offspring

| Metabolic phenotypes          | Association with obesity                                                                 | Exposure window | Metabolic changes and intrauterine environment                                                                 | Potential risks to offspring                                                                 | Possible mechanism                                                                                                                                 |
|------------------------------|--------------------------------------------------------------------------------------------|-----------------|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Maternal undernutrition      | This can occur in obesity due to poor dietary habits                                           | First and second trimesters | Lack of essential nutrients, imbalance of vitamin B<sub>12</sub> and folate levels, reduced folate levels         | Overeating, obesity, and diabetes in offspring, restricted fetal growth, risk of structural defects, development of neural tube defects | Hypothalamic apetite “programmed” to adapt, influences cellular growth and synthesis of amino acids, underdevelopment of neural tube                        |
| Gestational diabetes         |                                                                                             |                  | Overnutrition, increase in transfer of nutrients, hyperglycemia, stimulates fetal islets hyperinsulinemia          | Macrosomia at birth, fetal adiposity, increased risk of childhood obesity and diabetes         | Growth promoted in Insulin sensitive organs, alters structure and function of the pancreas, increases fat deposition                                       |
| Pregestational diabetes in mother | Associated with obesity as a risk factor.                                                    | First trimester  | Extratransfer of glucose                                                                                       | Increased risk of obesity in offspring and increased risk of diabetes                           | Hampers fetal β-cell formation, alters structure and function of the pancreas, stimulates fetal islets, and causes hyperinsulinemia                           |
| Visceral adiposity           | Associated with obesity                                                                      | First trimester  | Increase in insulin glucose levels and leptin; insulin resistance and procoagulant proteins cause impaired fibrinolysis and increased susceptibility to thrombosis, proinflammatory cytokines (tumor necrosis factor-α, interleukin-6), monocyte chemoattractant protein-1 | Risk of; macrosomic baby, neurodevelopmental disorders, type 2 diabetes, fetal death, birth defects, childhood asthma | Elevate progesterone concentrations (induce changes in brain development), fetal programming, increase risk of maternal diseases (e.g., pre-eclampsia), chronic inflammatory state |
Major Congenital Malformations

Complications such as fetal neural tube defects and other fetal anomalies have been investigated in relation to maternal obesity. An update of the latest evidence is discussed and presented in Table 2.

Neural Tube Defects

A meta-analysis of 12 studies (cohort and case-control) reported the odds of an infant being born with a neural tube defect (NTD) in overweight and obese mothers were odds ratio (OR) unadjusted: 1.22 (95% confidence interval [CI]: 0.99, 1.49, 12 studies), (overweight); OR unadjusted: 1.70 (95% CI: 1.34, 2.15, 11 studies) (obese); and OR unadjusted: 3.11 (95% CI: 1.75, 5.46, 5 studies) (severely obese) compared with mothers with normal prepregnancy BMI. The main limitation of these studies is the possibility of confounding by comorbidities such as diabetes, which although controlled for, may be undetected. A subsequent meta-analysis also demonstrated a statistically significant association between obese mothers and spina bifida, OR: 2.24 (95% CI: 1.86, 2.69; n = 863, five studies) and anencephaly OR: 1.39 (95% CI: 1.03, 1.87; n = 373, four studies). The reasons for the NTD association are not known. Obesity may be associated with factors that reduce folate levels and possible reasons for the increased risk of NTD in infants with obese mothers include altered glucose metabolism earlier in pregnancy, differences in nutritional requirements, and poor diet habits. In addition, recent genetic studies indicate that maternal metabolic genes associated with hyperglycemia and insulin resistance may interact to increase the risk of NTDs. Increased risk of NTDs has been attributed to lower levels of folate in obese women. However, an epidemiological study has shown no difference in the risk of the NTD spina bifida in the offspring of obese women who have taken a standard 400-µg dose of folic acid supplementation. Another hospital-based study found that the reduced risk of NTDs after supplementation with folic acid was weaker in obese mothers or mothers with an increased BMI (BMI ≥27). The Centre for Maternal and Child Enquiries and The Royal College of Obstetrics and Gynecology guidelines advise that obese women should take 5 mg of folic acid supplements daily, periconceptionally and throughout the first trimester. An audit of the implementation of the Centre for Maternal and Child Enquiries and the Royal College of Obstetrics and Gynecology recommendations for 5 mg folic acid supplementation has shown that these guidelines are not adhered to, and these groups have recommended that awareness be increased regarding the risk of NTDs in the obese women.

Congenital Heart Defects

A systematic review and meta-analysis of 24 studies has estimated the risk of congenital heart defects in offspring with nondiabetic but moderate and severely obese mothers to be: OR: 1.15 (95% CI: 1.11, 1.20; n = 1,176,564, 11 studies) and OR: 1.39 (95% CI: 1.31–1.47, n = 1,176,564, 5 studies), respectively. This risk was further increased when analyzed in women with gestational diabetes. Gestational diabetes is usually manifested in the second and third trimesters, after the fetal heart has already formed. However, fetal hyperinsulinemia and an altered intrauterine environment may have developed due to mild undiagnosed hyperglycemia earlier in pregnancy. The types of congenital defects that pregestanancy and gestational maternal obesity have been associated with include left ventricular outflow tract defects (hypoplastic left heart syndrome and aortic valve stenosis), anomalous pulmonary venous return; conotruncal defects (tetralogy of Fallot), septal defects (secundum atrial), and right ventricular outflow tract defects (pulmonary valve stenosis). However, these findings are not consistent in all studies and further high-quality epidemiologic studies are needed to clarify these associations.

Other Birth Defects

A systematic review and meta-analysis that examined 13 types of birth defects in addition to spina bifida and cardiac septal anomalies found a statistically significant increased risk of: cleft lip and palate (OR: 1.20; 95% CI: 1.03, 1.40, n = 1,188, three studies), cleft palate alone (OR: 1.23; 95% CI: 1.03–1.47, n = 865, three studies), and hydrocephaly (OR: 1.68; 95% CI: 1.19–2.36, n = 188, three studies) in infants born to obese mothers. This was not mirrored in infants of mothers who were overweight and no dose response relationship was evident between maternal BMI and risk of birth defects. Subsequent studies in Australia (n = 111), the United States (n = 14,319), and Saudi Arabia (n = 37,168) reported an association of pregestational obesity with orofacial clefts, limb reduction defects (over twofold), and urinary tract defects. In addition, the US study reported increased risks of anorectal atresia, hypospadia, limb reduction defects, diaphragmatic hernia, and omphalocele. The Australian study was limited by small sample size and the study conducted in Saudi Arabia did not adjust for pregestational diabetes.

Risk of Other Adverse Pregnancy Outcomes

Fetal Mortality

A meta-analysis of 38 cohort studies showed a moderate to strong increase in relative risk of fetal death, stillbirth, neonatal, perinatal, and infant death with an increase in maternal BMI. The relative risk of fetal death was 1.21 (95% CI: 1.09, 1.35; n = 690,622, seven studies); similar relative risks were found for stillbirth, perinatal, and neonatal deaths. The greatest risk was in severely obese women with a BMI of 40 or greater, which was estimated to be a two- to threefold higher risk than for those with a BMI of 20 or greater. Other meta-analyses report similar findings. Diabetes is often a comorbidity of obesity, and many of the studies investigating fetal death and obesity control for this factor; however, the rates of diabetes diagnosis reported in these studies were lower than those in the general literature, indicating that many cases of diabetes in these studies were likely not diagnosed. Despite this, a few studies that controlled for diabetes do show diabetes rates consistent with the general population, indicating that obesity is an independent risk factor for fetal death (Table 2).
| Outcome                  | Reference           | Association                                                                 | Postulated mechanism                                                                 | Issues and gaps in knowledge                                                                 |
|--------------------------|---------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Major congenital malformations |                     |                                                                              | Maternal hypoglycemia could interfere with glycolysis during embryogenesis, influencing the migration of neural crest cells essential for the development of the heart | Cases in most studies generally have low validity and ascertainment. There is a lack of consistency in studies. |
| Cardiac malformations    | Cai et al 2014\textsuperscript{57} | Meta-analysis; 24 studies:  
  Overweight BMI ≥25 <30  
  OR = 1.08\textsuperscript{a} (95% CI; 1.02, 1.15,  
  n = 798,054, 11 studies);  
  BMI ≥30 <35  
  Moderate (severe)  
  OR = 1.15\textsuperscript{a} (95% CI; 1.11, 1.20,  
  n = 735,281, five studies);  
  BMI ≥35 (severe)  
  OR = 1.39\textsuperscript{a}  
  (95% CI; 1.31, 1.47 n = 665,528, five studies) | | |
| Spina bifida             | Stothard et al 2009\textsuperscript{17} | Meta-analysis of 18 studies:  
  OR = 2.24\textsuperscript{a} (95% CI; 1.86, 2.69,  
  n = 863; five studies) | | |
| Anencephaly              | Stothard et al 2009\textsuperscript{17} | OR = 1.39\textsuperscript{a} (95% CI; 1.03, 1.87,  
  n = 373; four studies) | | |
| Other birth defects:     | Stothard et al 2009\textsuperscript{17} | Meta-analysis of 18 studies:  
  OR = 1.20\textsuperscript{a} (95% CI; 1.03, 1.40;  
  n = 1,188; three studies) | Obesity is a risk factor for diabetes; hence undiagnosed diabetes and hyperglycemia | Many studies used crude estimates and did not control for potential confounders.  
Some studies use small sample sizes.  
Further studies on dose response (i.e., varying BMI levels) are needed.  
Large, high-quality population-based studies are needed to confirm findings.  
Birth defects in elective terminations are not included in many studies.  
In Waller et al.\textsuperscript{18} controls are not matched to cases; there are demographic differences between cases and controls (e.g., maternal education).  
Definition of obesity due to BMI is not uniform across studies.  
Many studies use self-reported height and weight to calculate BMI can be over- or underestimated. There is a need for direct measurements. |
| Cleft lip and palate      |                     | OR = 1.23\textsuperscript{a} (95% CI; 1.03, 1.47  
  n = 865; three studies) | | |
| Cleft palate             |                     | OR = 1.68\textsuperscript{a} (95% CI; 1.19, 2.36;  
  n = 188; three studies) | | |
| Hydrocephaly             |                     |                                                                              | | |
| Outcome                        | Reference                     | Association                                                                 | Postulated mechanism                                                                                                                                                                                                 | Issues and gaps in knowledge                                                                                   |
|--------------------------------|-------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Anorectal atresia              | Waller et al 2007⁸             | (Excluded gestational diabetes  
\( n = 14,314 \))  
\( OR = 1.41 (95\% CI; 1.01, 1.97) \) |                                                                                                                                                                                                                          |                                                                                                                                                                         |
| Hypospadias                    |                               | OR = 1.21 (95\% CI; 0.93, 1.58)                                              |                                                                                                                                                                                                                          |                                                                                                                                                                         |
| Limb reduction defects         |                               | OR = 1.21 (95\% CI; 0.89, 1.63)                                              |                                                                                                                                                                                                                          |                                                                                                                                                                         |
| Diaphragmatic hernia           |                               | OR = 1.16 (95\% CI; 0.83, 1.96)                                              |                                                                                                                                                                                                                          |                                                                                                                                                                         |
| Omphalocele                    |                               | OR = 1.27 (95\% CI; 0.83, 1.96)                                              |                                                                                                                                                                                                                          |                                                                                                                                                                         |
| Other adverse pregnancy outcomes |                               |                                |                                                                                                                                                                                                                          |                                                                                                                                                                         |
| Fetal death                    | Aune et al 2014⁵²              | Meta-analysis of seven studies;  
\( n = 690,622 \)  
\( RR: 1.21 (95\% CI; 1.09, 1.35; \) \) \textit{\(n = 7\) studies} | Increased risk of preeclampsia, gestational diabetes, type 2 diabetes, gestational hypertension and congenital anomalies Increased inflammatory responses, vascular, endothelial dysfunction, altered lipid metabolism in obese women Increased risk of congenital malformations Hyperlipidemia can cause increased thromboxane production, which increases risk of placental thrombosis and decreases placental perfusion leading to infarction and abruption of placenta | Further studies are needed: to investigate mechanisms. Fetal deaths in low- and medium-income countries for generalizability. On gestational weight gain and fetal death are needed. |
| Fetal growth abnormalities: Macrosomia | Alberico et al 2014⁶⁹   | OR = 1.7 (95\% CI; 1.4, 2.2; cohort;  \( n = 14,109 \)) | Insulin resistance and glucose intolerance increase fetal glucose, insulin, steroids, and growth hormones, resulting in fetal fat deposition and accelerated birth weights | Further studies are needed to investigate the postulated mechanism, over successive generations. |
| Metabolic syndrome in offspring | Boney et al 2005⁷¹            | HR: 1.81 (95\% CI; 1.03, 3.19;  
\( n = 175; 6-11-year-old \)) | Fetal programming due to overnutrition, and imbalance of glucose, insulin, and inflammatory markers in the intrauterine environment | Require more studies to understand the fetal programming and transmission through successive generations. |
| Outcome | Reference | Association | Postulated mechanism | Issues and gaps in knowledge |
|---------|-----------|-------------|----------------------|-----------------------------|
| Neurodevelopmental outcomes | | | | |
| Child cognition | Basatemur et al 2013<sup>82</sup> | Increase in maternal BMI negatively affects child cognition at 5 and 7 years of offspring | Inflammatory intrauterine environment Increase in the permeability of the fetal blood-brain barrier Inflammation of the fetal brain Increase in leptin levels, which is involved in brain development Possibility of a common genetic pathway underlying obesity and poor mental health | Many unmeasured confounders related to neurodevelopment are not adjusted for in studies. Further studies are needed to establish this relationship. Some studies are small in size. Some studies used symptoms as an outcome and not the actual diagnosis of conditions such as ADHD. |
| Child cognition | Tanda et al 2013<sup>84</sup> | Offspring to obese mothers had reduced cognitive test scores | | |
| Child intelligence quotient | Neggers et al 2003<sup>86</sup> | Lower intelligence quotient in children of prepregnant obese mothers | | |
| Autism in offspring | Reynolds et al 2014<sup>89</sup> | Positive screen for autism OR: 9.875 (95% CI; 0.88, 3.70) n = 62 | | |
| Delayed mental development of offspring | Hinkle et al 2012<sup>90</sup> | Increase risk of delayed mental development (RR 1.38 (95% CI; 1.03, 1.84; cohort; n = 6,850) | | |
| ADHD in offspring | Chen et al 2014<sup>103</sup> | Increased risk of ADHD in offspring HR (obesity) = 1.64, (95% CI; 1.57, 1.73; cohort n = 673,632) | | |
| Teacher-rated high inattention | Rodriguez et al 2010<sup>102</sup> | OR: 2.09 (95% CI; 1.19, 4.82; cohort n = 1,714) | | |
| High ADHD symptom score | Rodriguez et al 2008<sup>91</sup> | OR:1.89 (95% CI; 1.13, 3.15; cohort n = 14,519) | | |

**Asthma**

| Asthma or wheeze | Forno et al 2014<sup>108</sup> | Meta-analysis of 14 studies n = 108,321 or (OR = 1.31; 95% CI: 1.16, 1.49) | Proinflammatory state in intrauterine environment can affect immune or pulmonary development | Other factors associated with obesity can also increase risk of asthma. Prospective randomized trials of maternal weight management are needed. |

Abbreviations: ADHD, attention deficit/hyperactivity disorder; BMI, body mass index; CI, confidence intervals; HR, hazards ratio; OR, odds ratio; RR, risk ratio.

<sup>*</sup>Unadjusted for potential confounders.
**Fetal Growth Abnormalities**

Maternal obesity OR: 1.7 (95% CI; 1.4, 2.2, n = 14,109) and extensive gestational weight gain OR: 1.9 (95% CI; 1.6, 2.2, n = 14,109) are independently associated with an increased risk of macrosomia and large for gestational age birth weight.\(^ {54,66-69}\) Insulin resistance and glucose intolerance increase fetal glucose, insulin, steroids, and growth hormones, resulting in fetal fat deposition and increased birth weights. Macrosomia and large for gestational age weight put the infant at risk of hyaline membrane disease OR: 2.14 (95% CI; 1.73, 2.66, n = 116,976), extended assisted ventilation OR: 1.71 (95% CI; 1.44, 2.04, n = 116,976), birth injury OR: 1.58 (95% CI; 1.37, 1.84, n = 116,976), and meconium aspiration OR: 1.42 (95% CI; 1.09, 1.89, n = 116,976) (\(\rightarrow \text{Table 2}\)).\(^ {70}\)

**Obesity and Metabolic Syndrome in the Offspring**

Children of obese mothers have increased risk of metabolic syndrome (hazard ratio [HR] = 1.81; 95% CI; 1.03–3.19)\(^ {71}\) and are more likely to be obese.\(^ {71-74}\) The molecular mechanisms by which maternal obesity might result in an increased risk of childhood obesity and metabolic syndrome are unknown. The rise in childhood obesity and metabolic syndrome coincides with an increased interest in the impact of the intrauterine environment on fetal gene expression and development.\(^ {75}\) It is thought that overnutrition of the fetus and the in utero environment are major contributors to obesity and metabolic disturbances in the offspring.\(^ {76,77}\) Nutritional imbalances during critical periods of fetal development are thought to program the fetus for metabolic syndrome later in life (\(\rightarrow \text{Table 2}\)).\(^ {78-80}\)

**Neurodevelopmental Outcomes**

There is evidence that maternal obesity may increase the risk of poor neurodevelopmental outcomes in full-term infants.\(^ {81,82}\) In animal models, maternal obesity has been associated with abnormal brain development, including impaired hippocampal growth, impaired hippocampus progenitor cell division, and neuronal production.\(^ {83}\) A possible explanation for this is the inflammatory process associated with maternal obesity causing inflammation of the fetal brain.

Epidemiologic studies suggest an association with lower general cognitive capabilities\(^ {84-86}\) and an increased incidence of autism spectrum disorders,\(^ {87-89}\) developmental delay,\(^ {90}\) and attention deficit/hyperactivity disorder (ADHD)\(^ {91}\); however, more evidence is required to substantiate these associations. A meta-analysis of 12 studies investigating the association of maternal obesity and neurodevelopmental outcomes in the offspring was not conclusive; however, authors suggested that there might be an increased risk of certain cognitive and psychiatric conditions across the lifespan.\(^ {81}\) It was noted that many of the studies possessed methodological limitations; for example, in one study the potential association between prepregnancy maternal obesity and reduced offspring intelligence quotient differed in different time periods, suggesting an unrecognized confounder may be affecting the result.\(^ {85}\)

A recent prospective cohort study (\(n = 62\)) investigating the risk of autism and maternal obesity found that maternal obesity was associated with an increased risk of developmental delay, poor language skills (in mothers with a BMI \(\geq 30\); \(\beta = -9.36\); 95% CI; \(-15.11, -3.61\); \(p = 0.002\)), and a positive screen for autism at the age of 2 years (OR = 9.88, 95% CI; 0.88, 3.70, \(p = 0.002\)).\(^ {86}\) However, this study had a small sample size, and was subject to misdiagnosis of autism due to ambiguity in diagnostic tests. The association between metabolic conditions during pregnancy and autism spectrum disorder and developmental disorders appears in another study, which examined obesity in combination with other metabolic conditions.\(^ {87,88}\) Further investigations using large population sizes and maternal obesity as the independent factor are required to explore this association further.

A prospective cohort study using data from Sweden, Denmark, and Finland investigated the association between maternal obesity and ADHD.\(^ {91}\) This study measured teacher-rated ADHD symptoms in 12,556 school-aged children. Maternal overweight or obesity was associated with a higher risk of having a child with ADHD symptoms compared with children of women of normal weight.\(^ {93}\) Although there is no clear mechanism known for this, the authors suggest several possibilities. Subjects with ADHD may share a common genetic trait that make individuals more prone to obesity.\(^ {92}\) Observations show an increased prevalence of obesity amongst those with mental disorders, and genetic studies link ADHD and obesity to the same dysfunction in dopaminergic and serotonergic systems.\(^ {93-97}\) Other causal theories include increased stress and cortisol levels, which can increase BMI and increase the risk of ADHD in the offspring\(^ {98,99}\); organic pollutants in the food chain, which are stored in adipose tissue\(^ {100}\), and increased synthesis of leptin.\(^ {101}\)

This study was then replicated with 1,714 Swedish preschool children within the same cohort and showed a higher risk of teacher-rated inattentive symptoms of ADHD among offspring overweight/obese mothers compared with normal-weight mothers.\(^ {102}\) A more recent population-based cohort study (\(n = 673,632\)) using linkage of Swedish national and regional registers reported an increased risk of offspring ADHD HR\(_{\text{overweight}}\) = 1.23, 95% CI; 1.18–1.27, \(p = 0.01\); HR\(_{\text{obesity}}\) = 1.64, 95% CI; 1.57–1.73, \(p = 0.01\) in association with obese mothers after adjustment for measured covariates. However, after making comparisons between siblings, this association was no longer present. The authors concluded that the association could be due to unmeasured familial confounding. Further studies are required to clarify this.\(^ {103}\)

Prepregnancy obesity could be linked to neurodevelopmental pathways through a variety of indirect noncausal pathways. Outcomes such as cognitive, emotional, and behavioral development could be linked to the postnatal period, familial risk, and child health problems, rather than the prenatal period. In addition, genetic and environmental confounders such as maternal cognitive problems, maternal psychiatric conditions, and poor socioeconomic status.
may contribute to neurodevelopmental outcomes. Such factors can act individually to increase risk and also interact with each other making interpretations of studies in this area challenging. Neurodevelopmental outcomes are usually detected later in childhood. The older the child becomes the longer the exposure time to postnatal environmental and other external risk factors, making it more difficult to determine the association between the effects of the fetal intrauterine environment and neurodevelopmental outcomes. To minimize these challenges due to genetic and environmental risks factors, future studies may benefit from examining subsequent pregnancies in the same mother-partner pair. Although studies suggest a link between prepregnancy obesity and neurodevelopmental outcomes, because of the limitations in study designs, findings should be interpreted with caution. More data are needed to confirm these associations.

**Asthma in Offspring**

There is growing evidence that maternal obesity in pregnancy and gestational weight gain is associated with increased risk of asthma in offspring and may slow down improvement in airway hyper-reactivity that usually occurs in children with asthma as they grow older. It is thought that different dietary patterns or proinflammatory states associated with obesity may affect fetal immune or pulmonary development, thus leading to asthma. A meta-analysis of 14 studies, reported that children whose mothers were obese during pregnancy were at higher risk of asthma or wheeze (Table 2). The results showed higher odds of asthma or wheeze ever (OR: 1.31; 95% CI: 1.16–1.49) or current (OR: 2.21; 95% CI: 1.07–1.37). Each 1 kg/m² increase in maternal BMI was associated with a 2 to 3% increase in odds of childhood asthma. A major limitation of these studies is that although maternal obesity is a risk factor for childhood obesity, other factors such as childhood obesity can also increase the risk of asthma. More prospective studies investigating the association of maternal obesity and asthma in the offspring are needed.

**Recommendations and Conclusion**

**Interventions**

Interventions targeting maternal obesity have the potential to improve outcomes in the offspring and subsequent future generations. Although some countries have produced guidelines and recommendations for lifestyle interventions during pregnancy, there is no international consensus and no standardized management strategy specifically for obese pregnant women.

The best window of opportunity to prevent fetal programming is in the periconceptional period. This is the period when gametogenesis, fertilization, implantation, embryogenesis, and placentation occur. It is ideal that the metabolic environment is stabilized at this time; hence, interventions such as preconception assessment and counselling should be implemented prior to pregnancy. Once women are pregnant, interventions should aim to minimize gestational weight gain and correct metabolic imbalances.

There is lack of evidence to recommend the ideal weight gain for obese women during pregnancy. Evidence for effectiveness of lifestyle and dietary interventions is not clear. Example of dietary interventions that have been shown to be successful in controlling weight gain during pregnancy in randomized trials of obese nondiabetic pregnant women include a series of 10 consultations of 1 hour each, dietary education with daily food records reviewed at prenatal visits, a series of four dietary counseling sessions combined with a free 6-month membership to fitness centers that include weekly training sessions with a physiotherapist.

Guidance from the American Congress of Obstetricians and Gynecologists recommend all pregnant women, including those with increased BMI, are encouraged to participate in regular moderate-intensive physical activity for 30 minutes daily. There is evidence to suggest that physical activity in healthy pregnant women is associated with improved maternal glucose control and reduced risk of macrosomia and adiposity in the offspring. In addition, physical activity is effective in reducing the incidence of type 2 diabetes in high-risk populations and improves insulin sensitivity independent of weight loss. The risk of developing gestational diabetes during pregnancy is decreased with physical activity, particularly if practiced regularly prior to pregnancy. Although there are studies that demonstrate the benefits of physical activity in pregnancy, an effective intervention needs to be implemented. Current studies investigating the impact of such interventions are small in subject size, with poor adherence to physical activity. A pilot randomized controlled trial of 183 subjects, investigated the impact of combined physical activity and dietary intervention on pregnancy and infant outcomes (e.g., glucose homeostasis, macrosomic babies). The intervention failed to impact on the level of physical activity, and there were no differences in physical activity between the control and intervention group. There is a need for a better understanding of the barriers of obese women engaging in physical activity during pregnancy to develop the interventions.

Current intervention studies do not focus on obese women who are at high risk, for example, women with a higher percentage of visceral adiposity, or a history of hypertension, cardiovascular disease, and diabetes. More intensive interventions should be targeted for these high-risk populations. Other measures such as waist circumference (before conception and/or very early in pregnancy) in addition to BMI should be used to screen for women with visceral adiposity. Interventions to correct metabolic imbalances such as blood glucose control should be placed at preconception.

**Future Studies**

Most studies investigating maternal obesity rely on self-reports of weight and height to calculate BMI, which can be over- or underestimated affecting the risk estimates. Furthermore, BMI does not measure adiposity. Hence future studies will benefit, using direct measures and by including measures.
of adiposity such as waist circumference. There is a need for more high-quality studies designed to adjust for confounders, including genetic and environmental risk factors. A better understanding of the mechanisms of the intrauterine environment and other mechanisms underlying the association with neurodevelopmental and asthma outcomes are needed. To prevent adverse outcomes of maternal obesity, more interventional studies are needed to help women reach and maintain health weights.

In summary, recent studies strengthen the evidence of an association between maternal obesity and neurodevelopmental and asthma outcomes. Evidence of an association of maternal obesity to neurodevelopmental adverse events and asthma is emerging. Further exploration of these outcomes is required.

Acknowledgments
A. B. is a consultant for plaintiffs in the litigation involving antidepressants and birth defects. N. I. has no conflicts of interest to declare that are directly or relevant to the content of this study.

References
1 Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States, 1991–1998. JAMA 1999;282(16):1519–1522
2 Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999;282(16):1523–1529
3 Martorell R, Khan LK, Hughes ML, Grummer-Strawn LM. Obesity in Latin American women and children. J Nutr 1998;128(9):1464–1473
4 Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. JAMA 2012;307(5):483–490
5 Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009–2010: Centers for Disease Control and Prevention: 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22617494. Accessed June 21, 2015
6 Kanagalingam MG, Forouhi NG, Greer IA, Sattar N. Changes in booking body mass index over a decade: retrospective analysis from a Glasgow Maternity Hospital. BJOG 2005;112(10):1431–1433
7 Obesity: Preventing and Managing the Global Epidemic. Report of the WHO Consultation on Obesity. 1997. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_894_(part1).pdf?ua=1&ua=1. Accessed January 22, 2015
8 Sebire NJ, Jolly M, Harris JP, et al. Maternal obesity and pregnancy outcome: a study of 287,213 pregnancies in London. Int J Obes Relat Metab.Disord 2001;25(8):1175–1182
9 O’Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic overview. Epidemiology 2003;14(3):368–374
10 Chu SY, Callaghan WM, Kim SY, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care 2007;30(8):2070–2076
11 Poston L, Harthooran LF, Van Der Beek EM; Contributors to the ILSI Europe Workshop. Obesity in pregnancy: implications for the mother and lifelong health of the child. A consensus statement. Pediatr Res 2011;69(2):175–180
12 Waller DK, Mills JL, Simpson JL, et al. Are obese women at higher risk for producing malformed offspring? Am J Obstet Gynecol 1994;170(2):541–548
13 Rasmussen SA, Chu SY, Kim SY, Schmid CH, Lau J. Maternal obesity and risk of neonatal tube defects: a meta-analysis. Am J Obstet Gynecol 2008;198(6):611–619
14 Smith SA, Hulsey T, Goodnight W. Effects of obesity on pregnancy. J Obstet Gynecol Neonatal Nurs 2008;37(2):176–184
15 Weight Gain During Pregnancy. Weight Gain during Pregnancy: Reexamining the Guidelines; 2009. Available at: http://www.nap.edu/catalog/12584/weight-gain-during-pregnancy-reexaming-the-guidelines. Accessed November 1, 2014
16 Castro LC, Avina RL. Maternal obesity and pregnancy outcomes. Curr Opin Obstet Gynecol 2002;14(6):601–606
17 Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA 2009;301(6):636–650
18 Waller DK, Shaw GM, Rasmussen SA, et al; National Birth Defects Prevention Study. Prepregnancy obesity as a risk factor for structural birth defects. Arch Pediatr Adolesc Med 2007;161(8):745–750
19 Fernandez-Twinn DS, Ozanne SE. Early life nutrition and metabolic programming. Ann N Y Acad Sci 2010;1212:78–96
20 Correa-Branco A, Keating E, Martel F. Maternal undernutrition and fetal developmental programming of obesity: the glucocorticoid connection. Reprod Sci 2015;22(2):138–145
21 Madan JC, Davis JM, Craig WY, et al. Maternal obesity and markers of inflammation in pregnancy. Cytokine 2009;47(1):61–64
22 Catalanò PM. The impact of gestational diabetes and maternal obesity on the mother and her offspring. J Dev Orig Health Dis 2010;1(4):208–215
23 Mehta S, Farmer JA. Obesity and inactivation: a new look at an old problem. Curr Atheroscler Rep 2007;9(2):134–138
24 Greenberg AS, Obin MS. The role of adipose tissue in inflammation and metabolism. Am J Clin Nutr 2006;83(2):4615–4655
25 Ramsay JE, Ferrell WR, Crawford J, Wallace AM, Greer IA, Sattar N. Maternal obesity is associated with dysregulation of metabolic, vascular, and inflammatory pathways. J Clin Endocrinol Metab 2002;87(9):4231–4237
26 Wolf M, Kettye L, Sandler L, Ecker JL, Roberts J, Thadhani R. Obesity and preeclampsia: the potential role of inflammation. Obstet Gynecol 2001;98(5, Pt 1):757–762
27 Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003;288(1):76–79
28 Yoon BH, Romero R, Kim CJ, et al. High expression of tumor necrosis factor-alpha and interleukin-6 in periventricular leukomalacia. Am J Obstet Gynecol 1997;177(2):406–411
29 McDonald DG, Kelehan P, McMenamin JB, et al. Placental fetal thrombocytopenic vasculopathy is associated with neonatal encephalopathy. Hum Pathol 2004;35(7):875–880
30 Berry SM, Romero R, Gomez R, et al. Premature parturition is characterized by in utero activation of the fetal immune system. Am J Obstet Gynecol 1995;173(4):1320–1322
31 Gomez R, Romero R, Ghezzi F, Yoon BH, Mazor M, Berry SM. The fetal inflammatory response syndrome. Am J Obstet Gynecol 1998;179(1):194–202
32 Romero R, Gomez R, Ghezzi F, et al. A fetal systemic inflammatory response is followed by the spontaneous onset of preterm parturition. Am J Obstet Gynecol 1998;179(1):186–193
33 Leviton A, Dammann O, Coagulation, inflammation, and the risk of neonatal white matter damage. Pediatr Res 2004;55(4):541–545
34 Dammann O, Leviton A. Inflammation, brain damage and visual dysfunction in preterm infants. Semin Fetal Neonatal Med 2006;11(5):363–368
35 Pohlemeier WE, Xie F, Kurz SG, Lu N, Wood JR. Progressive obesity alters the steroidogenic response to ovulatory stimulation and increases the abundance of mRNAs stored in the ovulated oocyte. Mol Reprod Dev 2014;81(8):735–747
36 Morrison JL, Duffield JA, Muhlhauser BS, Gentili S, McMillen IC. Fetal growth restriction, catch-up growth and the early origins of insulin resistance and visceral obesity. Pediatr Nephrol 2010;25(4):669–677
37 Gupta A, Srinivasan M, Thamadiikot S, Patel MS. Hypothalamic alterations in fetuses of high fat diet-fed obese female rats. J Endocrinol 2009;200(3):293–300
38 Sullivan EL, Smith MS, Grove KL. Perinatal exposure to high-fat diet programs energy balance, metabolism and behavior in adulthood. Neuroendocrinology 2011;93(1):1–8
39 Stachowiak EK, Oommen S, Vasu VT, et al. Maternal obesity affects gene expression and cellular development in fetal brains. Nutr Neurosci 2013;16(3):96–103
40 Wells JC. The thrifty phenotype as an adaptive maternal effect. Biol Reprod Camb Philos Soc 2007;82(1):143–172
41 Janssens I, Heymsfield SB, Allison DB, Kotler DP, Ross R. Body mass index and waist circumference independently contribute to the prediction of nonabdominal, abdominal subcutaneous, and visceral fat. Am J Clin Nutr 2002;75(4):683–688
42 Després JP. Is visceral obesity the cause of the metabolic syndrome? Ann Med 2006;38(1):52–63
43 Ross R, Freeman J, Hudson R, Janssens I. Abdominal obesity, muscle composition, and insulin resistance in premenopausal women. J Clin Endocrinol Metab 2002;87(11):5044–5051
44 Després JP, Moorjani S, Ferland M, et al. Adipose tissue distribution and plasma lipoprotein levels in obese women. Importance of intra-abdominal fat. Arteriosclerosis 1989;9(2):203–210
45 Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. Lancet 1993;341(8850):938–941
46 Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. N Engl J Med 1976;295(7):349–353
47 Pomeroy J, Renström F, Gradmark AM, et al. Maternal physical activity and insulin action in pregnancy and their relationships with infant body composition. Diabetes Care 2013;36(2):267–269
48 Committee on Obstetric Practice; American College of Obstetricians and Gynecologists. ACOG committee opinion. Exercise during pregnancy and the postpartum period. Number 267, January 2002. Int J Gynaecol Obstet 2002;77(1):79–81
49 Hendricks KA, Nuno OM, Suarez L, Larsen R. Effects of hyperinsulinemia and obesity on risk of neural tube defects among Mexican Americans. Epidemiology 2001;12(6):630–635
50 Carmichael SL, Shaw GM, Selvin S, Schaffer DM. Diet quality and risk of neural tube defects. Med Hypotheses 2003;60(3):351–355
51 Carmichael SL, Shaw GM, Schaffer DM, Laurent C, Selvin S. Dieting behaviors and risk of neural tube defects. Am J Epidemiol 2003;158(12):1127–1131
52 Lupo PJ, Mitchell LE, Canfield MA, et al; National Birth Defects Prevention Study. Maternal-fetal metabolic gene-gene interactions and risk of neural tube defects. Mol Genet Metab 2014;111(1):46–51
53 Mojtabai R. Body mass index and serum folate in childbearing age women. Eur J Epidemiol 2004;19(11):1029–1036
54 Parker SE, Yazdy MM, Tinker SC, Mitchell AA, Werler MM. The impact of folic acid intake on the association among diabetes mellitus, obesity, and spina bifida. Am J Obstet Gynecol 2013;209(3):239.e1–239.e8
55 Wang M, Wang ZP, Gao LJ, Gong R, Sun XH, Zhao ZT. Maternal body mass index and the association between folic acid supple-
ments and neural tube defects. Acta Paediatr 2013;102(9):908–913
56 Centre for Maternal and Child Enquiries and Royal College of Obstetricians and Gynaecologists. Management of Women with Obesity in Pregnancy 2012. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/cancercohortguideli-
nemenagementwomenobesitypregnancy.pdf. Accessed June 21, 2015
57 Cai GJ, Sun XX, Zhang L, Hong Q. Association between maternal body mass index and congenital heart defects in offspring: a systematic review. Am J Obstet Gynecol 2014;211(2):91–117
58 Gilboa SM, Correa A, Botto LD, et al; National Birth Defects Prevention Study. Association between prepregnancy body mass index and congenital heart defects. Am J Obstet Gynecol 2010;202(1):51.e1–51.e10
59 Mills JL, Treonelle J, Conley MR, Carter T, Druschel CM. Maternal obesity and congenital heart defects: a population-based study. Am J Clin Nutr 2010;91(6):1543–1549
60 Balaha MH, Ali WH, Al Aswad LH, Al Moghannum MS, Hashim I. Maternal obesity predict isolated birth defects in live births in Eastern Province of Saudi Arabia. J Matern Fetal Neonatal Med 2012;25(7):924–929
61 Oddy WH, De Klerk NH, Miller M, Payne J, Bower C. Association of maternal prepregnancy weight with birth defects: evidence from a case-control study in Western Australia. Aust N Z J Obstet Gynaecol 2009;49(1):11–15
62 Aune D, Saugstad OD, Henriksen T, Tonstad S. Maternal body mass index and the risk of fetal death, stillbirth, and infant death: a systematic review and meta-analysis. JAMA 2014;311(15):1536–1546
63 Flendy V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet 2011;377(9774):1331–1340
64 Bianco AT, Smilen SW, Davis Y, Lopez S, Lapinski R, Lockwood CJ. Pregnancy outcome and weight gain recommendations for the morbidly obese woman. Obstet Gynecol 1998;91(1):97–102
65 Kumari AS. Pregnancy outcome in women with morbid obesity. Int J Gynaecol Obstet 2001;73(2):101–107
66 Lu GC, Rouse DJ, DuBard M, Cliver S, Kimberlin D, Hauth JC. The effect of the increasing prevalence of maternal obesity on perinatal morbidity. Am J Obstet Gynecol 2001;185(4):845–849
67 Lederman SA. Pregnancy weight gain and postpartum loss: avoiding obesity while optimizing the growth and development of the fetus. J Am Med Womens Assoc 2001;56(2):53–58
68 Ray JG, Vermeulen MJ, Shapiro JL, Kershole AB; Diabetes Endo-
crine Pregnancy Outcome Study in Toronto. Maternal and neo-
natal outcomes in pregestational and gestational diabetes mellitus, and the influence of maternal obesity and weight gain: the DEPOSIT study. QJM 2001;94(7):347–356
69 Alberico S, Montico M, Barresi V, et al; Multicentre Study Group on Mode of Delivery in Friuli Venezia Giulia. The role of gestational diabetes, prepregnancy body mass index and gestational weight gain on the risk of newborn macrosomia: results from a prospective multicentre study. BMC Pregnancy Childbirth 2014;14:23
70 Salihu HM, Weldeselasse HE, Rao K, Marty PJ, Whiteman VE. The Centre for Maternal and Child Enquiries and Royal College of Obstetricians and Gynaecologists. Management of Women with Obesity in Pregnancy 2012. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/cancercohortguideli-
nemenagementwomenobesitypregnancy.pdf. Accessed June 21, 2015
71 Boney CM, Verma A, Tucker R, Voehr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 2005;115(3):e290–e296
72 Crespo PS, Prieto Perera JA, Lodeiro FA, Azaurre LA. Metabolic syndrome in childhood. Public Health Nutr 2007;10(10A):1121–1125
73 Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/
Prepregnancy Maternal Obesity

Lam LT, Yang L. Overweight/obesity and attention deficit hyperactivity disorder: a new view of “comfort food.” Proc Natl Acad Sci U S A 2002; 7(8): 829–830

Dallman MF, Pecoraro N, Akana SF, et al. Chronic stress and obesity: a new view of “comfort food.” Proc Natl Acad Sci U S A 2003; 100(20): 11696–11701

Van den Bergh BR, Mulder EJ, Mennes M, Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. Neurosci Biobehav Rev 2005; 28(2): 237–258

Lee DH, Jacobs DR, Porta M. Association of serum concentrations of persistent organic pollutants with the prevalence of learning disability and attention deficit disorder. J Epilepsy Community Health 2007; 61(7): 591–596

Hendler I, Blackwell SC, Mehta SH, et al. The levels of leptin, adiponectin, and resistin in normal weight, overweight, and obese pregnant women with and without preeclampsia. Am J Obstet Gynecol 2005; 193(3, Pt 2): 979–983

Rodriguez A. Maternal pre-pregnancy obesity and risk for inattention and negative emotionality in children. J Child Psychol Psychiatry 2010; 51(2): 134–143

Chen Q, Sjölander A, Långström N, et al. Maternal pre-pregnancy body mass index and offspring attention deficit hyperactivity disorder: a population-based cohort study using a sibling-comparison design. Int J Epidemiol 2014; 43(1): 83–90

Thomsen SF, van der Sluis S, Kyvik KO, Skytte A, Skadhauge LR, Backer V. Increase in the heritability of asthma from 1994 to 2003 among adolescent twins. Respir Med 2011; 105(8): 1147–1152

Cohen RT, Raby BA, Van Steen K, et al; Childhood Asthma Management Program Research Group. In utero smoke exposure and impaired response to inhaled corticosteroids in children with asthma. J Allergy Clin Immunol 2010; 126(3): 491–497

Caudri D, Savinije OE, Smit HA, et al. Perinatal risk factors for wheezing phenotypes in the first 8 years of life. Clin Exp Allergy 2013; 43(12): 1395–1405

Guerra S, Sartini C, Mendez M, et al. Maternal prepregnancy obesity is an independent risk factor for frequent wheezing in infants by age 14 months. Paediatr Perinat Epidemiol 2013; 27(1): 100–108

Forno E, Young OM, Kumar R, Simhan H, Celedón JC. Maternal obesity in pregnancy, gestational weight gain, and risk of childhood asthma. Pediatrics 2014; 133(4): e535–e546

Bogaerts A, Devlieger R, Van den Bergh BR, Witters I. Obesity and pregnancy, an epidemiological and intervention study from a psychosocial perspective. Facts Views Vis Obgyn 2014; 6(2): 81–95

Scott C, Andersen CT, Valdez N, et al. No global consensus: a cross-sectional survey of maternal weight policies. BMC Pregnancy Childbirth 2014; 14: 167

Yajnik CS. Transmission of obesity-adiposity and related disorders from the mother to the baby. Ann Nutr Metab 2014; 64 (Suppl 1): 8–17

Vesco KK, Karanja N, King JC, et al. Healthy Moms, a randomized trial to promote and evaluate weight maintenance among obese pregnant women: study design and rationale. Contemp Clin Trials 2012; 33(4): 777–785

Wolff S, Legarth J, Vangsgaard K, Toubro S, Astrup A. A randomized trial of the effects of dietary counseling on gestational weight gain and glucose metabolism in obese pregnant women. Int J Obes 2008; 32(3): 495–501
Thornton YS, Smarkola C, Kopacz SM, Ishoof SB. Perinatal outcomes in nutritionally monitored obese pregnant women: a randomized clinical trial. J Natl Med Assoc 2009;101(6):569–577

Vinter CA, Jensen DM, Ovesen P, Beck-Nielsen H, Jørgensen JS. The LiP (Lifestyle in Pregnancy) study: a randomized controlled trial of lifestyle intervention in 360 obese pregnant women. Diabetes Care 2011;34(12):2502–2507

Barakat R, Cordero Y, Coteron J, Luaces M, Montejo R. Exercise during pregnancy improves maternal glucose screen at 24-28 weeks: a randomised controlled trial. Br J Sports Med 2012;46(9):656–661

Gillies CL, Abrams KR, Lambert PC, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 2007;334(7588):299

Ross R, Janssen I, Dawson J, et al. Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial. Obes Res 2004;12(5):789–798

Tobias DK, Zhang C, van Dam RM, Bowers K, Hu FB. Physical activity before and during pregnancy and risk of gestational diabetes mellitus: a meta-analysis. Diabetes Care 2011;34(1):223–229

Hayes L, Bell R, Robson S, Poston L; UPBEAT Consortium. Association between physical activity in obese pregnant women and pregnancy outcomes: the UPBEAT pilot study. Ann Nutr Metab 2014;64(3-4):239–246

Stafne SN, Salvesen KA, Romundstad PR, Eggebø TM, Carlsten SM, Mørkved S. Regular exercise during pregnancy to prevent gestational diabetes: a randomized controlled trial. Obstet Gynecol 2012;119(1):29–36