

## PRENATAL DETERMINANTS OF CHILDHOOD OBESITY: A REVIEW OF RISK FACTORS

Xiang-Peng Liao<sup>1,2#</sup>, Yamei Yu<sup>3#</sup>, Isabelle Marc<sup>4</sup>, Lise Dubois<sup>3</sup> Nadia Abdelouahab<sup>2</sup>, Luigi Bouchard<sup>5</sup>,  
Yan-Ting Wu<sup>6, 7</sup>, Fengxiu Ouyang<sup>8</sup>, Heng-Feng Huang<sup>6, 7</sup>, William D. Fraser<sup>2\*</sup>

<sup>1</sup>Department of Pediatrics, Shanghai Gongli Hospital, The Second Military Medical University, Shanghai, China

<sup>2</sup>Centre Hospitalier Universitaire de Sherbrooke (CHUS) Research Centre, and Department of Obstetrics and Gynecology, Université de Sherbrooke, Quebec, Canada

<sup>3</sup>School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Canada

<sup>4</sup>Centre Hospitalier Universitaire de Québec Research Centre and Department of Pediatrics, Faculty of Medicine, Université Laval, Quebec, Canada

<sup>5</sup>Department of Medical Biology, CIUSSS-SLSJ, Université de Sherbrooke, Saguenay, Canada

<sup>6</sup>International Peace Maternity & Child Health Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

<sup>7</sup>Institute of Embryo-Fetal Original Adult Diseases, Shanghai Jiao Tong University School of Medicine, Shanghai, China

<sup>8</sup>Ministry of Education-Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

#The two first authors contributed equally to the manuscript.

\*Corresponding author: William D. Fraser

Centre Hospitalier Universitaire de Sherbrooke (CHUS) Research Centre, and Department of Obstetrics and Gynecology, Université de Sherbrooke, Sherbrooke, Quebec, Canada  
William.Fraser@USherbrooke.ca  
Address: 3001, 12e avenue Nord, Sherbrooke, Québec, Canada J1H 5N4  
Tel: 1-819-346-1110  
Fax: 1-819-820-6434

## ABSTRACT

Childhood obesity is a predictor of adult obesity, and has its roots in the pre-pregnancy or pregnancy period. This review presents an overview of the prenatal risk factors for childhood obesity, which were categorized into two groups: biological risk factors (maternal pre-pregnancy body mass index, gestational weight gain, diabetes in pregnancy, and caesarean section), and environmental and behavioural risk factors (maternal smoking and exposure to obesogens, maternal dietary patterns, maternal intestinal microbiome and antibiotics exposure, and maternal psychosocial stress). Identifying modifiable predisposing prenatal factors for obesity will inform further development of interventions to prevent obesity over the life course, and future directions for research and intervention are discussed.

**Keywords:** Risk factors, Obesity, Pregnancy, Body mass index, Childhood

## 1. INTRODUCTION

Obesity is generally defined as a condition in which the degree of excess body fat has the potential to negatively impact on health outcomes (WHO 2017). Body mass index (BMI) is a commonly used measure to assess obesity ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) or overweight ( $\text{BMI} \geq 25 \text{ kg/m}^2 < 30$ ) in adults. In children, sex and age are taken into consideration to assess overweight and obesity. The World Health Organization (WHO) has defined age- and sex-specific weight-for-height cutoffs from children aged 0 to 5 years (WHO 2016; 2017). The International Obesity Task Force (IOTF) provides age and sex specific BMI cutoffs for children aged 2 to 18 years (Cole et al. 2000). Some Asian countries use lower BMI cutoffs than those applied in Europe and North America (Chen et al. 2012; de Wilde et al. 2013), as some Asians have higher weight-related disease risks at lower BMIs (Misra 2015).

There is an increasing prevalence of obesity, and globally, obesity has almost doubled since 1980 (Ng et al. 2014; WHO 2014). Childhood obesity predicts the risk of adulthood obesity (Whitaker et al. 1997), and is associated with increased morbidity from non-communicable diseases. In a meta-analysis of 37 studies, high childhood BMI was found to be a strong positive association with adult obesity (OR 5.21;

95% CI 4.50, 6.02) (Simmonds et al. 2015); and high childhood BMI was found to increase the risk of adult diabetes (OR 1.70; 95% CI 1.30, 2.22), coronary heart disease (CHD) (OR 1.20; 95% CI 1.10, 1.31), adult hypertension at age 12 years and over (OR 1.29; 95% CI 1.19,1.40), and various cancers (Llewellyn et al. 2016). Ending childhood obesity is a global public health priority as proposed by the WHO (WHO 2016).

Accumulating evidence shows that non-communicable diseases and health in adults are related to fetal and infant environments (Barker 2004). The mechanisms through which fetal exposures contribute to the development of obesity are complex and poorly understood. These might include gene-environment interactions, the epigenome and multiple environmental factors, to which the maternal/fetal unit is exposed such as energy-dense diets, physical inactivity, and obesogenic environmental chemicals (Bell et al. 2005; Bouret et al. 2015), as well as the interactions between these factors. Furthermore, sex/gender, race/ethnicity, age and exposures during puberty may be related to the development of obesity (Han et al. 2010). Genetics plays a key role throughout the life course. For example, genome-wide studies (Horikoshi et al. 2016) demonstrated that fetal genetic variations contribute to approximately 15% of variance in birthweight, and genetic determinants of susceptibility to obesity in adulthood begin acting in early life (Warrington et al. 2015). A study conducted in twins (Silventoinen et al. 2016) found that, among populations of different ethnicities, environmental effects on BMI variation were more obvious in mid-childhood, whereas genetic factors played a major role in BMI variation in adolescence, with estimated heritability increasing from 0.42 in boys and 0.41 in girls at 4 years of age to 0.75 in both sexes at age 19 years. Meanwhile, a recent large genome-wide association study identified maternal genes that can be associated with offspring birthweight (Beaumont et al. 2018).

The Developmental Origins of Health and Disease (DOHaD) hypothesis suggests that environmental factors acting during a critical window of development can change the capacity of the organism to cope with its environment in later life (Gluckman and Hanson 2006). Thus, strategies to modify exposure to risk factors during prenatal care may be central to early obesity prevention (Gillman and Ludwig 2013; Kemp et al. 2012). Based on systematic reviews, meta-analyses, and the results of large cohort studies

from the last decade, we provide a narrative review of the epidemiological evidence on prenatal determinates of childhood obesity. Stressing modifiable elements for further study and prevention from post-conception to birth, this review classifies prenatal determinants as: 1) biological risk factors: maternal pre-pregnancy BMI, excessive gestational weight gain (GWG), diabetes in pregnancy, and caesarean section; and 2) environmental and behavioural risk factors: maternal smoking and exposure to obesogens, maternal dietary patterns, maternal intestinal microbiome and antibiotics exposure, and maternal psychosocial stress.

## **2. BIOLOGICAL RISK FACTORS**

### **2.1. Maternal pre-pregnancy BMI**

Higher maternal pre-pregnancy BMI increases the risk of childhood obesity. The Avon Longitudinal Study of Parents and Children in the United Kingdom with 8234 children in cohort aged 7 years found that maternal obese prepregnancy was associated with offspring obesity (OR 4.25; 95% CI 3.28, 6.44), while both parents obese prepregnancy further increased the risk offspring obesity (OR 10.44; 95% CI 5.11, 21.32) (Reilly, et al. 2005). A meta-analysis of 45 studies (Yu et al. 2013) found that, compared to subjects with normal BMI, pre-pregnancy maternal overweight or obesity increased the risk of overweight (OR 1.95; 95% CI 1.77, 2.13) and obesity (OR 3.06; 95% CI 2.68, 3.49) in offspring from infancy to adolescence.

Studies in industrialized countries have examined the relationship between maternal pre-pregnancy BMI and body composition in their offspring, and evidence to date suggests that higher maternal pre-pregnancy BMI is associated with higher offspring adiposity. A meta-analysis of 20 studies (Castillo-Laura et al. 2015) found that, compared to infants of women with normal pre-pregnancy BMI, infants born to overweight and obese women had higher fat mass and percent body fat, and standardized mean differences during the period of 1 month to 6 years of age were 0.38kg (95% CI 0.26 kg, 0.50 kg) in fat mass, and 0.31 percentage (95% CI 0.19, 0.42) in percent body fat, respectively. The association of maternal obesity with greater offspring adiposity can be mediated via increased DNA methylation (Sharp

et al. 2015), and animal studies found that maternal obesity can alter endoplasmic reticulum homeostasis in offspring pancreas (Soeda et al. 2016).

## 2.2. Excessive GWG

Excessive GWG defined by the recommendation of The Institute of Medicine, USA (Rasmussen et al. 2009), is associated with an increased risk of overweight and obesity in childhood. A systematic review and meta-analysis (Mamun et al. 2014) showed that pregnant women with excessive GWG had an increased risk of obesity in the offspring (OR 1.40; 95% CI 1.23, 1.59), while women who had inadequate GWG had a 14% (OR 0.86; 95% CI 0.78, 0.94) reduction in the risk of future obesity in the offspring, with the effects remaining similar across different age groups of early childhood (<5 years), early to late adolescence (5-18 years), and adulthood ( $\geq 18$  years). Other systematic reviews observed similar effects with ORs of 1.21 (95% CI 1.05, 1.40) (Tie et al. 2014) and 1.38 (95% CI 1.21, 1.57) (Nehring et al. 2013) for the effects of excessive GWG on offspring obesity, and 0.91 (95% CI 0.85, 0.98) (Nehring et al. 2013) for inadequate GWG on childhood overweight. Furthermore, the association between GWG and later offspring BMI may be stronger during early- and mid-pregnancy than late pregnancy, as suggested by a systematic review (Lau et al. 2014).

Excessive GWG can be associated with increased adipose tissue deposition in newborns and childhood. One systematic review and meta-analysis (Castillo-Laura et al. 2015) of 7 studies, mainly conducted in industrialized countries, suggested positive relationships between maternal GWG and both fat mass and percent body fat.

A direct effect of excessive maternal energy intake is excessive GWG while dietary restriction may have the opposite effect. A systematic review of 10 clinical trials (Tanentsapf et al. 2011) of dietary interventions designed to prevent excess GWG showed significantly reduced total GWG associated with the intervention, with a mean difference of -1.92 kg (95% CI -3.65 kg, -0.19 kg). Another systematic review and meta-analysis of 24 randomized controlled trials (Muktabhant et al. 2015) found that diet or exercise interventions, either alone or in combination, reduced the risk of excessive GWG by 20% overall

(average RR 0.8; 95%CI 0.73, 0.87). A recent systematic review and meta-analysis (Group 2017) reported a mean reduction of GWG of -0.70 kg (95% CI -0.92 kg, -0.48 kg) in the groups exposed to the diet and physical activity intervention.

### **2.3. Diabetes in pregnancy**

Pregnancy complications such as gestational diabetes (GDM), maternal hypertension and preeclampsia may be causally associated with birthweight (Patro Golab et al. 2018; Tyrrell et al. 2016), but currently more studies stress the effects of GDM on childhood obesity than other pregnancy complications. Infants of mothers who suffered from gestational diabetes (GDM) have a greater risk of developing obesity than infants of mothers without diabetes. One systematic review including 12 studies and an updated review including 7 studies (Kim et al. 2011; Kim et al. 2012) found a positive association between GDM and offspring overweight and obesity. The association was attenuated after adjustments for maternal pre-pregnancy BMI but generally remained statistically significant. A recent meta-analysis (Logan et al. 2017) including 35 studies found that infants of diabetic mothers (type 1, type 2, and gestational) had higher fat mass (difference 83 g; 95% CI 49 g, 117 g), and percent body fat (difference 2.2%; 95% CI 1.1, 3.2) in infancy; and subgroup analyses indicated that fat mass in infancy was greater, both in infants of mothers with GDM (difference of 62 g; 95% CI 29 g, 94 g) and type 1 diabetes (difference of 268 g; 95% CI 139 g, 397 g).

### **2.4. Caesarean section**

There is some evidence that caesarean section may be a risk factor for childhood obesity. A large prospective Chinese birth cohort study (Li et al. 2014) including 181,380 children observed that, compared to vaginal delivery, children born by non-medically indicated caesarean delivery due to sociocultural factors had an increased risk of overweight (OR 1.18; 95% CI 1.00, 1.41) at age 3–7 years. A systematic review and meta-analysis (Li et al. 2013) found an increased risk of overweight and obesity (OR 1.33; 95% CI 1.19, 1.48) in offspring delivered by caesarean section compared to children born vaginally. A similar association was observed in another systematic review and meta-analysis (Kuhle et al.

2015), demonstrating an increased risk of obesity (RR 1.34; 95% CI 1.18, 1.51) in children born by caesarean section compared to vaginal birth. Meanwhile, studies conducted in Denmark (Ajslev et al. 2011), Brazil (Barros et al. 2012) and Germany (Pei et al. 2014) show the effect size of caesarean section to childhood obesity is attenuated after adjusting for confounders, and influenced by sex and age of children.

Caesarean section is usually accompanied with antibiotic use, which may affect microbiota in the offspring (Rutayisire et al. 2016). Meanwhile, caesarean section is negatively associated with early breastfeeding (Prior et al. 2012), which is a significant protective factor for childhood obesity (WHO 2016; Yan et al. 2014). The effects of cesarean section may at least partially be explained by the impact on the microbiota and breastfeeding (Ajslev et al. 2011; Kuhle et al. 2015).

### **3. ENVIRONMENTAL AND BEHAVIOURAL RISK FACTORS**

#### **3.1. Maternal smoking and exposure to obesogens**

Obesogens are foreign chemical compounds that induce obesity by increasing fat cells and/or the storage of fat in existing adipocytes. Currently identified obesogens include more than 20 chemicals (Heindel et al. 2015; Holtcamp 2012). Obesogens sources range from exposure to environmental chemicals in everyday life to the side effects of pharmaceutical drugs. The obesogen hypothesis suggests that the increased use of synthetic organic and inorganic chemicals over the last decades has contributed to the global obesity epidemic (Baillie-Hamilton 2002). Obesogens might increase the risk of childhood obesity by disrupting hormone-mediated processes in the womb (Braun 2017). Except for nicotine exposure due to smoking, the impact of prenatal exposure to obesogens in childhood obesity is underexplored.

##### **3.1.1. Maternal smoking**

There is robust evidence on the association between maternal smoking in pregnancy and childhood obesity. One early meta-analysis of 16 observational studies (Oken et al. 2008) found that compared with no maternal smoking, maternal smoking during pregnancy was associated with an

increased risk of offspring overweight at aged 3-33 years (OR 1.40; 95% CI 1.26, 1.55). This observation is reinforced by the findings of a recent systematic review and meta-analysis (Rayfield and Plugge 2017), demonstrating that maternal smoking in pregnancy was associated with an increased risk for childhood overweight (OR 1.37, 95% CI 1.28, 1.46,) and childhood obesity (OR 1.55, 95% CI 1.40, 1.73) in the offspring. Another meta-analysis (Riedel et al. 2014) including 109,838 mother-child pairs reported similar effects for maternal smoking during pregnancy on offspring overweight (OR 1.33; 95% CI 1.23, 1.44) and obesity (OR 1.60; 95% CI 1.37, 1.88), and maternal smoking effects were stronger than the paternal smoking effects on offspring overweight (OR 1.07; 95% CI 1.00, 1.16), and obesity (OR 1.23; 95% CI 1.10, 1.38). These results suggest a higher direct intrauterine impact of maternal smoking compared to paternal or household smoking.

### 3.1.2. Environmental obesogens

Epidemiological studies suggest that several environmental pollutants are associated with rapid childhood growth. But most of human studies have been cross-sectional in design, and reports from longitudinal studies involved with prenatal maternal exposure are limited (Heindel et al. 2015; Ranciere et al. 2015). In the case of perfluoroalkyl substances (PFAS) exposure, recent studies strongly support that prenatal maternal exposure is associated with excess adiposity and obesity in childhood (Braun 2017; Braun et al. 2016; Hartman et al. 2017; Mora et al. 2017). For example, studies from the USA found that higher prenatal perfluoroalkyl substances (PFAS) exposure was associated with a rapid increase in BMI of children between 2-8 years (Braun et al. 2016), and small increases in adiposity measurements in mid-childhood girls (Mora et al. 2017). With respect to prenatal bisphenol A (BPA) exposure, a systematic review with meta-analysis showed that higher urinary bisphenol A (BPA) concentration was associated with excess childhood adiposity (Ranciere et al. 2015).

Prenatal exposures to other environmental chemicals that are possibly associated with childhood obesity include dichlorodiphenyldichloroethylene (DDE) (Tang-Peronard et al. 2014; Vafeiadi et al. 2015; Valvi et al. 2014), hexachlorobenzene (HCB) (Vafeiadi et al. 2015; Valvi et al. 2014), polycyclic



aromatic hydrocarbon (PAH) (Rundle et al. 2012), and polybrominated diphenylethers (PBDE) (Braun et al. 2016; Erkin-Cakmak et al. 2015; Hartman et al. 2017; Tang-Peronard et al. 2014). A pooled analysis of seven European birth cohorts found that dichlorodiphenyldichloroethylene (DDE) was associated with a significant increase in weight-for-age z-score in infants (Iszatt et al. 2015). However, findings on the effect of prenatal obesogen exposure on child weight are inconsistent across studies (Liu and Peterson 2015; Woo Baidal et al. 2016).

### **3.2. Maternal dietary patterns**

Dietary patterns are defined in terms of the quantities, proportions, variety or combinations of food consumption (Committee 2015). Some studies have found positive associations between the quantities of maternal intake of protein and fatty acid during pregnancy and the risk of childhood obesity (Brion et al. 2010; Fekete et al. 2015; Mennitti et al. 2015; Robinson and Godfrey 2008). Changes in fatty acid intake during pregnancy and lactation may lead to permanent changes in appetite control in the offspring (Kabaran and Besler 2015). However, recent systematic reviews and meta-analyses (Hauer et al. 2013; Stratakis et al. 2014) found no conclusive evidence supporting the association between maternal long-chain polyunsaturated fatty acid intake during pregnancy and childhood obesity.

The sharp increase in dietary intake of fructose and high-fructose corn syrup in recent decades is also suspected to be associated with obesity prevalence (Marriott et al. 2009; Sloboda et al. 2014). Through its metabolic effects, high fructose exposure during critical periods of development of the fetus, as well as the neonate and infant, is suggested to impact the long-term development of obesity (Goran et al. 2013), and animal studies support this link (Howie et al. 2009; Regnault et al. 2013). Meanwhile, a systematic review (Morgan 2013) found that consumption of high-fructose corn syrup beverages in children can contribute to childhood obesity.

### **3.3. Maternal intestinal microbiome and exposure to antibiotics**

Recent studies support the findings that certain gut microbiome profiles can significantly contribute to weight gain and childhood obesity. The mechanisms may include the regulation of energy

recovery and fat storage from the diet, the role of inflammation in metabolic phenotypes, and microbial translocation (Cox and Blaser 2013; Sekirov et al. 2010). Human studies have observed differences between obese and lean groups in microbiota composition, functional genes and metabolic activities (Gerard 2016). Exposure to antibiotics in early life may be associated with increased risk of childhood obesity (Cox and Blaser 2015; Paliy et al. 2014). For example, one study of Danish mother-child dyads followed through 7 years of age showed that children whose mothers were exposed to antibiotics during the second or third trimesters of pregnancy were at increased risk of obesity (RR 1.84; 95% CI 1.33, 2.54) (Mueller et al. 2015). Another study of Danish school children found that prenatal exposure to systemic antibacterials was associated with an increased risk of overweight (OR 1.26; 95% CI 1.10, 1.45) and obesity (OR 1.29; 95% CI 1.03, 1.62) (Mor et al. 2015). In contrast, one study in the USA found that childhood antibiotic use – not prenatal antibiotic exposure – was associated with childhood obesity risk at 3 years of age (Poulsen et al. 2017).

Probiotics are live microorganisms, whereas prebiotics are ingredients that promote the growth of beneficial intestinal microorganisms (Klaenhammer et al. 2012). Mother-child studies demonstrate that *Bifidobacterium* strains in infants, one major component of the intestinal microbiota, can be derived from the mother's intestine through vaginal delivery (Makino et al. 2013), and administration of probiotics to pregnant women can cause infantile colonization, persisting for 6 months or more (Schultz et al. 2004). While clinical trials are underway (Luoto et al. 2010), there is as yet insufficient evidence to assess the long-term impact of probiotics on childhood obesity.

### 3.4. Maternal psychosocial stress

Prenatal maternal psychosocial stress can profoundly influence endocrine function over the lifecourse (Kapoor et al. 2006). Severe maternal psychosocial stress can be associated with subsequent offspring alterations in the regulation of hypothalamic-pituitary-adrenal axis (Entringer et al. 2009), and glucose-insulin metabolic function (Entringer et al. 2008).

Depending on severity and timing of stress, and sex of the offspring, exposure to maternal

psychosocial stress may be positively associated with childhood overweight and obesity (Entringer 2013; Ertel et al. 2010; Ingstrup et al. 2012). One meta-analysis of 17 studies (Tate et al. 2015) found that both in cross-sectional and longitudinal observations, higher levels of prenatal psychological stress were associated with higher risk of childhood obesity. Furthermore, the effect of prenatal stress on offspring obesity may be more evident as the child's age advances (Tate et al. 2015). For example, The Quebec Ice Storm Study (Liu et al. 2016) found dose-response effects between prenatal stress level and the child's BMI and waist-to-height ratio, with the positive associations tending to be more obvious as children become older.

#### 4. CONCLUSION AND RECOMMENDATIONS

Findings from systematic reviews, meta-analyses, large observational studies, and randomized controlled trials, show that maternal exposures during the pre-pregnancy and pregnancy periods contribute to the etiology of childhood obesity (see Table 1).

It should be noted that prenatal biological risk factors can interact with environmental and behavioural risk factors, and prenatal risk factors can also interact with postnatal risk factors, collectively contributing to obesity development. For example, maternal smoking during pregnancy and GWG can both independently contribute to birthweight, and maternal smoking often affects GWG (Davies and Abernethy 1976); high birthweight is also associated with an increased risk of childhood obesity (Schellong et al. 2012; Yu et al. 2011). Meanwhile, maternal smoking during pregnancy can be associated with rapid weight gain from birth to early infancy (Mine et al. 2017), and the latter can be a significant predictor of adiposity in later life (Zheng et al. 2018).

Besides examining the effect of individual risk factors, further well-designed studies are needed to explore the interactive and cumulative effects of these risk factors, and the causal relationship over the life course. The variations in effect sizes and conflicting results across studies may partly be due to the differences in BMI cutoffs for overweight or obesity, definitions and measurements of variables, participant inclusion criteria, the effects of confounding variables such as social-economic background,

lifestyle and other environmental factors.

The identification of modifiable risk factors is important to the development of interventions to prevent and manage obesity in early life and beyond. An optimal approach to obesity prevention during prenatal care could be an integrated management of preconception, pregnancy and childbirth, as well as obesity prevention measures in the adolescent or young adult population long before pregnancy (WHO2003; Ma et al. 2016), focusing on healthy nutrition, physical activity and appropriate weight management, emotional and psychological well-being, avoidance of exposure to smoking and environmental obesogens, comprehensive management of GDM, limited antibiotic use, and appropriate birthing options including the reduction of caesarean section for non-medical reasons.

Findings from this study point to future avenues for research and intervention. First, there is a need for research focusing on the long-term cumulative effects of individual and contextual factors, with a life course perspective that starts in pre-pregnancy or early pregnancy and continues through childhood and adulthood, and that targets different levels of woman and child, family, and community. Second, because childhood obesity is linked with certain non-communicable diseases in adulthood (Llewellyn et al. 2016), a comprehensive approach to investigation should include longitudinal examination of body composition and metabolic biomarkers as well. Third, for the purpose of elucidating growth trajectories and unlocking the complex mechanism, it is significant that more studies from developing countries, and integration and cooperation across countries into research networks with the harmonization and pooling of information between studies (Fortier et al. 2010). Fourth, strategies for effective intervention should include a multifaceted approach with audit and feedback, prospectively identifying specific barriers and facilitators, and adaptation to the context (individual, local, national, and international) (Chaillet et al. 2006). The Healthy Life Trajectories Initiative issued by The Canadian Institute of Health Research is underway, which could be a model of this integrated strategy (<http://www.cihr-irsc.gc.ca/e/49510.html>).

## ACKNOWLEDGEMENTS

This review was conducted in preparation for submission of the team grant: Healthy Life Trajectories

Initiative, and supported by the Canadian Institutes of Health Research (Grant number 36924), and the National Natural Science Foundation of China (grant number 81661128010).

**Author contribution:** All authors contributed to literature search, the writing and revision of the manuscript, and approved it for publication.

**Conflict of interest:** The authors declare that there is no conflict of interest.

## REFERENCES

- Ajslev, T.A., Andersen, C.S., Gamborg, M., Sorensen, T.I., and Jess, T. 2011. Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. *Int J Obes (Lond)* **35**(4): 522-529. doi: 10.1038/ijo.2011.27.
- Baillie-Hamilton, P.F. 2002. Chemical toxins: a hypothesis to explain the global obesity epidemic. *Journal of alternative and complementary medicine (New York, N.Y.)* **8**(2): 185-192. doi: 10.1089/107555302317371479.
- Barker, D.J. 2004. Developmental origins of adult health and disease. *Journal of epidemiology and community health* **58**(2): 114-115.
- Barros, F.C., Matijasevich, A., Hallal, P.C., Horta, B.L., Barros, A.J., Menezes, A.B., et al. 2012. Cesarean section and risk of obesity in childhood, adolescence, and early adulthood: evidence from 3 Brazilian birth cohorts. *The American journal of clinical nutrition* **95**(2): 465-470. doi: 10.3945/ajcn.111.026401.
- Beaumont, R.N., Warrington, N.M., Cavadino, A., Tyrrell, J., Nodzinski, M., Horikoshi, M., et al. 2018. Genome-wide association study of offspring birth weight in 86 577 women identifies five novel loci and highlights maternal genetic effects that are independent of fetal genetics. *Human molecular genetics* **27**(4): 742-756. doi: 10.1093/hmg/ddx429.
- Bell, C.G., Walley, A.J., and Froguel, P. 2005. The genetics of human obesity. *Nature reviews. Genetics* **6**(3): 221-234. doi: 10.1038/nrg1556.
- Bouret, S., Levin, B.E., and Ozanne, S.E. 2015. Gene-environment interactions controlling energy and glucose homeostasis and the developmental origins of obesity. *Physiological reviews* **95**(1): 47-82. doi: 10.1152/physrev.00007.2014.

- Braun, J.M. 2017. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. *Nature reviews. Endocrinology* **13**(3): 161-173. doi: 10.1038/nrendo.2016.186.
- Braun, J.M., Chen, A., Romano, M.E., Calafat, A.M., Webster, G.M., Yolton, K., et al. 2016. Prenatal perfluoroalkyl substance exposure and child adiposity at 8 years of age: The HOME study. *Obesity (Silver Spring)* **24**(1): 231-237. doi: 10.1002/oby.21258.
- Brion, M.J., Ness, A.R., Rogers, I., Emmett, P., Cribb, V., Davey Smith, G., et al. 2010. Maternal macronutrient and energy intakes in pregnancy and offspring intake at 10 y: exploring parental comparisons and prenatal effects. *The American journal of clinical nutrition* **91**(3): 748-756. doi: 10.3945/ajcn.2009.28623.
- Castillo-Laura, H., Santos, I.S., Quadros, L.C., and Matijasevich, A. 2015. Maternal obesity and offspring body composition by indirect methods: a systematic review and meta-analysis. *Cadernos de saude publica* **31**(10): 2073-2092. doi: 10.1590/0102-311X00159914.
- Chaillet, N., Dube, E., Dugas, M., Audibert, F., Tourigny, C., Fraser, W.D., et al. 2006. Evidence-based strategies for implementing guidelines in obstetrics: a systematic review. *Obstet Gynecol* **108**(5): 1234-1245. doi: 10.1097/01.AOG.0000236434.74160.8b.
- Chen, S., Binns, C.W., and Zhang, Y. 2012. The importance of definition in diagnosing obesity: a review of studies of children in China. *Asia-Pacific journal of public health* **24**(2): 248-262. doi: 10.1177/1010539512441617.
- Cole, T.J., Bellizzi, M.C., Flegal, K.M., and Dietz, W.H. 2000. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* **320**(7244): 1240-1243. doi: 10.1136/bmj.320.7244.1240.
- Dietary Guidelines Advisory Committee. 2015. Scientific report of the 2015 dietary guidelines advisory committee. Washington (DC): USDA and US Department of Health and Human Services.
- Cox, L.M., and Blaser, M.J. 2013. Pathways in microbe-induced obesity. *Cell metabolism* **17**(6): 883-894. doi: 10.1016/j.cmet.2013.05.004.
- Cox, L.M., and Blaser, M.J. 2015. Antibiotics in early life and obesity. *Nature reviews. Endocrinology* **11**(3): 182-190. doi: 10.1038/nrendo.2014.210.
- Davies, D.P., and Abernethy, M. 1976. Cigarette smoking in pregnancy: Associations with maternal weight gain and fetal growth. *Lancet* **1**(7956): 385-387.
- de Wilde, J.A., van Dommelen, P., and Middelkoop, B.J. 2013. Appropriate body mass index cut-offs to determine thinness, overweight and obesity in South Asian children in the Netherlands. *PLoS One* **8**(12): e82822. doi: 10.1371/journal.pone.0082822.
- Entringer, S. 2013. Impact of stress and stress physiology during pregnancy on child metabolic function and obesity risk. *Current opinion in clinical nutrition and metabolic care* **16**(3): 320-327. doi: 10.1097/MCO.0b013e32835e8d80.
- Entringer, S., Kumsta, R., Hellhammer, D.H., Wadhwa, P.D., and Wust, S. 2009. Prenatal exposure to maternal psychosocial stress and HPA axis regulation in young adults. *Hormones and behavior* **55**(2): 292-298. doi: 10.1016/j.yhbeh.2008.11.006.

- Entringer, S., Wust, S., Kumsta, R., Layes, I.M., Nelson, E.L., Hellhammer, D.H., et al. 2008. Prenatal psychosocial stress exposure is associated with insulin resistance in young adults. *Am J Obstet Gynecol* **199**(5): 498.e491-497. doi: 10.1016/j.ajog.2008.03.006.
- Erkin-Cakmak, A., Harley, K.G., Chevrier, J., Bradman, A., Kogut, K., Huen, K., et al. 2015. In utero and childhood polybrominated diphenyl ether exposures and body mass at age 7 years: the CHAMACOS study. *Environ Health Perspect* **123**(6): 636-642. doi: 10.1289/ehp.1408417.
- Ertel, K.A., Koenen, K.C., Rich-Edwards, J.W., and Gillman, M.W. 2010. Antenatal and postpartum depressive symptoms are differentially associated with early childhood weight and adiposity. *Paediatr Perinat Epidemiol* **24**(2): 179-189. doi: 10.1111/j.1365-3016.2010.01098.x.
- Fekete, K., Gyorei, E., Lohner, S., Verduci, E., Agostoni, C., and Decsi, T. 2015. Long-chain polyunsaturated fatty acid status in obesity: a systematic review and meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity* **16**(6): 488-497. doi: 10.1111/obr.12280.
- Fortier, I., Burton, P.R., Robson, P.J., Ferretti, V., Little, J., L'Heureux, F., et al. 2010. Quality, quantity and harmony: the DataSHaPER approach to integrating data across bioclinical studies. *Int J Epidemiol* **39**(5): 1383-1393. doi: 10.1093/ije/dyq139.
- Gerard, P. 2016. Gut microbiota and obesity. *Cellular and molecular life sciences : CMLS* **73**(1): 147-162. doi: 10.1007/s00018-015-2061-5.
- Gillman, M.W., and Ludwig, D.S. 2013. How early should obesity prevention start? *N Engl J Med* **369**(23): 2173-2175. doi: 10.1056/NEJMp1310577.
- Gluckman, P.D., and Hanson, M.A. 2006. *The developmental origins of health and disease: an overview.* Cambridge University Press, Cambridge. pp. 1-5.
- Goran, M.I., Dumke, K., Bouret, S.G., Kayser, B., Walker, R.W., and Blumberg, B. 2013. The obesogenic effect of high fructose exposure during early development. *Nature reviews. Endocrinology* **9**(8): 494-500. doi: 10.1038/nrendo.2013.108.
- Weight Management in Pregnancy (i-WIP) Collaborative Group. 2017. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. *BMJ* **358**. doi: 10.1136/bmj.j3119.
- Han, J.C., Lawlor, D.A., and Kimm, S.Y.S. 2010. Childhood obesity. *The Lancet* **375**(9727): 1737-1748. doi: 10.1016/s0140-6736(10)60171-7.
- Hartman, T.J., Calafat, A.M., Holmes, A.K., Marcus, M., Northstone, K., Flanders, W.D., et al. 2017. Prenatal Exposure to Perfluoroalkyl Substances and Body Fatness in Girls. *Child Obes* **13**(3): 222-230. doi: 10.1089/chi.2016.0126.
- Hauner, H., Brunner, S., and Amann-Gassner, U. 2013. The role of dietary fatty acids for early human adipose tissue growth. *The American journal of clinical nutrition* **98**(2): 549s-555s. doi: 10.3945/ajcn.112.040733.
- Heindel, J.J., Newbold, R., and Schug, T.T. 2015. Endocrine disruptors and obesity. *Nature reviews. Endocrinology* **11**(11): 653-661. doi: 10.1038/nrendo.2015.163.

- Holtcamp, W. 2012. Obesogens: an environmental link to obesity. *Environ Health Perspect* **120**(2): a62-68. doi: 10.1289/ehp.120-a62.
- Horikoshi, M., Beaumont, R.N., Day, F.R., Warrington, N.M., Kooijman, M.N., Fernandez-Tajes, J., et al. 2016. Genome-wide associations for birth weight and correlations with adult disease. *Nature* **538**(7624): 248-252. doi: 10.1038/nature19806.
- Howie, G.J., Sloboda, D.M., Kamal, T., and Vickers, M.H. 2009. Maternal nutritional history predicts obesity in adult offspring independent of postnatal diet. *The Journal of physiology* **587**(Pt 4): 905-915. doi: 10.1113/jphysiol.2008.163477.
- Ingstrup, K.G., Schou Andersen, C., Ajslev, T.A., Pedersen, P., Sorensen, T.I., and Nohr, E.A. 2012. Maternal Distress during Pregnancy and Offspring Childhood Overweight. *J Obes* **2012**: 462845. doi: 10.1155/2012/462845.
- Iszatt, N., Stigum, H., Verner, M.A., White, R.A., Govarts, E., Murinova, L.P., et al. 2015. Prenatal and Postnatal Exposure to Persistent Organic Pollutants and Infant Growth: A Pooled Analysis of Seven European Birth Cohorts. *Environ Health Perspect* **123**(7): 730-736. doi: 10.1289/ehp.1308005.
- Kabaran, S., and Besler, H.T. 2015. Do fatty acids affect fetal programming? *Journal of health, population, and nutrition* **33**: 14. doi: 10.1186/s41043-015-0018-9.
- Kapoor, A., Dunn, E., Kostaki, A., Andrews, M.H., and Matthews, S.G. 2006. Fetal programming of hypothalamo-pituitary-adrenal function: prenatal stress and glucocorticoids. *The Journal of physiology* **572**(Pt 1): 31-44. doi: 10.1113/jphysiol.2006.105254.
- Kemp, M.W., Kallapur, S.G., Jobe, A.H., and Newnham, J.P. 2012. Obesity and the developmental origins of health and disease. *J Paediatr Child Health* **48**(2): 86-90. doi: 10.1111/j.1440-1754.2010.01940.x.
- Kim, S.Y., England, J.L., Sharma, J.A., and Njoroge, T. 2011. Gestational diabetes mellitus and risk of childhood overweight and obesity in offspring: a systematic review. *Exp Diabetes Res* **2011**: 541308. doi: 10.1155/2011/541308.
- Kim, S.Y., Sharma, A.J., and Callaghan, W.M. 2012. Gestational diabetes and childhood obesity: what is the link? *Current opinion in obstetrics & gynecology* **24**(6): 376-381. doi: 10.1097/GCO.0b013e328359f0f4.
- Klaenhammer, T.R., Kleerebezem, M., Kopp, M.V., and Rescigno, M. 2012. The impact of probiotics and prebiotics on the immune system. *Nature reviews. Immunology* **12**(10): 728-734. doi: 10.1038/nri3312.
- Kuhle, S., Tong, O.S., and Woolcott, C.G. 2015. Association between caesarean section and childhood obesity: a systematic review and meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity* **16**(4): 295-303. doi: 10.1111/obr.12267.
- Lau, E.Y., Liu, J., Archer, E., McDonald, S.M., and Liu, J. 2014. Maternal weight gain in pregnancy and risk of obesity among offspring: a systematic review. *J Obes* **2014**: 524939. doi: 10.1155/2014/524939.
- Li, H., Ye, R., Pei, L., Ren, A., Zheng, X., and Liu, J. 2014. Caesarean delivery, caesarean delivery on maternal request and childhood overweight: a Chinese birth cohort study of 181 380 children. *Pediatr Obes* **9**(1): 10-16. doi: 10.1111/j.2047-6310.2013.00151.x.



Li, H.T., Zhou, Y.B., and Liu, J.M. 2013. The impact of cesarean section on offspring overweight and obesity: a systematic review and meta-analysis. *Int J Obes (Lond)* **37**(7): 893-899. doi: 10.1038/ijo.2012.195.

Liu, G.T., Dancause, K.N., Elgbeili, G., Laplante, D.P., and King, S. 2016. Disaster-related prenatal maternal stress explains increasing amounts of variance in body composition through childhood and adolescence: Project Ice Storm. *Environmental research* **150**: 1-7. doi: 10.1016/j.envres.2016.04.039.

Liu, Y., and Peterson, K.E. 2015. Maternal Exposure to Synthetic Chemicals and Obesity in the Offspring: Recent Findings. *Current environmental health reports* **2**(4): 339-347. doi: 10.1007/s40572-015-0068-6.

Llewellyn, A., Simmonds, M., Owen, C.G., and Woolacott, N. 2016. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity* **17**(1): 56-67. doi: 10.1111/obr.12316.

Logan, K.M., Gale, C., Hyde, M.J., Santhakumaran, S., and Modi, N. 2017. Diabetes in pregnancy and infant adiposity: systematic review and meta-analysis. *Archives of disease in childhood. Fetal and neonatal edition* **102**(1): F65-f72. doi: 10.1136/archdischild-2015-309750.

Luoto, R., Kalliomaki, M., Laitinen, K., and Isolauri, E. 2010. The impact of perinatal probiotic intervention on the development of overweight and obesity: follow-up study from birth to 10 years. *Int J Obes (Lond)* **34**(10): 1531-1537. doi: 10.1038/ijo.2010.50.

Ma, R.C.W., Schmidt, M.I., Tam, W.H., McIntyre, H.D., and Catalano, P.M. 2016. Clinical management of pregnancy in the obese mother: before conception, during pregnancy, and post partum. *Lancet Diabetes Endocrinol* **4**(12): 1037-1049. doi: 10.1016/s2213-8587(16)30278-9.

Makino, H., Kushiro, A., Ishikawa, E., Kubota, H., Gawad, A., Sakai, T., et al. 2013. Mother-to-infant transmission of intestinal bifidobacterial strains has an impact on the early development of vaginally delivered infant's microbiota. *PLoS One* **8**(11): e78331. doi: 10.1371/journal.pone.0078331.

Mamun, A.A., Mannan, M., and Doi, S.A. 2014. Gestational weight gain in relation to offspring obesity over the life course: a systematic review and bias-adjusted meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity* **15**(4): 338-347. doi: 10.1111/obr.12132.

Marriott, B.P., Cole, N., and Lee, E. 2009. National estimates of dietary fructose intake increased from 1977 to 2004 in the United States. *The Journal of nutrition* **139**(6): 1228s-1235s. doi: 10.3945/jn.108.098277.

Mennitti, L.V., Oliveira, J.L., Morais, C.A., Estadella, D., Oyama, L.M., Oller do Nascimento, C.M., et al. 2015. Type of fatty acids in maternal diets during pregnancy and/or lactation and metabolic consequences of the offspring. *The Journal of nutritional biochemistry* **26**(2): 99-111. doi: 10.1016/j.jnutbio.2014.10.001.

Mine, T., Tanaka, T., Nakasone, T., Itokazu, T., Yamagata, Z., and Nishiwaki, Y. 2017. Maternal smoking during pregnancy and rapid weight gain from birth to early infancy. *Journal of epidemiology / Japan Epidemiological Association* **27**(3): 112-116. doi: 10.1016/j.je.2016.10.005.

Misra, A. 2015. Ethnic-Specific Criteria for Classification of Body Mass Index: A Perspective for Asian Indians and American Diabetes Association Position Statement. *Diabetes technology & therapeutics* **17**(9): 667-671. doi: 10.1089/dia.2015.0007.

- Mor, A., Antonsen, S., Kahlert, J., Holsteen, V., Jorgensen, S., Holm-Pedersen, J., et al. 2015. Prenatal exposure to systemic antibacterials and overweight and obesity in Danish schoolchildren: a prevalence study. *Int J Obes (Lond)* **39**(10): 1450-1455. doi: 10.1038/ijo.2015.129.
- Mora, A.M., Oken, E., Rifas-Shiman, S.L., Webster, T.F., Gillman, M.W., Calafat, A.M., et al. 2017. Prenatal Exposure to Perfluoroalkyl Substances and Adiposity in Early and Mid-Childhood. *Environ Health Perspect* **125**(3): 467-473. doi: 10.1289/ehp246.
- Morgan, R.E. 2013. Does consumption of high-fructose corn syrup beverages cause obesity in children? *Pediatr Obes* **8**(4): 249-254. doi: 10.1111/j.2047-6310.2013.00173.x.
- Mueller, N.T., Whyatt, R., Hoepner, L., Oberfield, S., Dominguez-Bello, M.G., Widen, E.M., et al. 2015. Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity. *Int J Obes (Lond)* **39**(4): 665-670. doi: 10.1038/ijo.2014.180.
- Muktabhant, B., Lawrie, T.A., Lumbiganon, P., and Laopaiboon, M. 2015. Diet or exercise, or both, for preventing excessive weight gain in pregnancy. *The Cochrane database of systematic reviews* **6**(6): CD007145. doi: 10.1002/14651858.CD007145.pub3.
- Nehring, I., Lehmann, S., and von Kries, R. 2013. Gestational weight gain in accordance to the IOM/NRC criteria and the risk for childhood overweight: a meta-analysis. *Pediatr Obes* **8**(3): 218-224. doi: 10.1111/j.2047-6310.2012.00110.x.
- Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., et al. 2014. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* **384**(9945): 766-781. doi: 10.1016/s0140-6736(14)60460-8.
- Oken, E., Levitan, E.B., and Gillman, M.W. 2008. Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis. *Int J Obes (Lond)* **32**(2): 201-210. doi: 10.1038/sj.ijo.0803760.
- World Health Organization (WHO). 2003. Integrated management of pregnancy and childbirth. Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice. Geneva: Department of Reproductive Health and Research, Family and Community Health, World Health Organization: 180.
- World Health Organization (WHO). 2014. Global status report on noncommunicable diseases 2014.
- World Health Organization (WHO). 2016. Report of the Commission on Ending Childhood Obesity.
- World Health Organization (WHO). 2017. Obesity and overweight Fact sheet [accessed October 2017 2017].
- Paliy, O., Piyathilake, C.J., Kozyrskyj, A., Celep, G., Marotta, F., and Rastmanesh, R. 2014. Excess body weight during pregnancy and offspring obesity: potential mechanisms. *Nutrition (Burbank, Los Angeles County, Calif.)* **30**(3): 245-251. doi: 10.1016/j.nut.2013.05.011.
- Patro Golab, B., Santos, S., Voerman, E., Lawlor, D.A., Jaddoe, V.W.V., and Gaillard, R. 2018. Influence of maternal obesity on the association between common pregnancy complications and risk of childhood obesity: an individual participant data meta-analysis. *The Lancet. Child & adolescent health* **2**(11): 812-821. doi: 10.1016/s2352-4642(18)30273-6.

- Pei, Z., Heinrich, J., Fuertes, E., Flexeder, C., Hoffmann, B., Lehmann, I., et al. 2014. Cesarean delivery and risk of childhood obesity. *J Pediatr* **164**(5): 1068-1073 e1062. doi: 10.1016/j.jpeds.2013.12.044.
- Poulsen, M.N., Pollak, J., Bailey-Davis, L., Hirsch, A.G., Glass, T.A., and Schwartz, B.S. 2017. Associations of prenatal and childhood antibiotic use with child body mass index at age 3 years. *Obesity (Silver Spring)* **25**(2): 438-444. doi: 10.1002/oby.21719.
- Prior, E., Santhakumaran, S., Gale, C., Philipps, L.H., Modi, N., and Hyde, M.J. 2012. Breastfeeding after cesarean delivery: a systematic review and meta-analysis of world literature. *The American journal of clinical nutrition* **95**(5): 1113-1135. doi: 10.3945/ajcn.111.030254.
- Ranciere, F., Lyons, J.G., Loh, V.H., Botton, J., Galloway, T., Wang, T., et al. 2015. Bisphenol A and the risk of cardiometabolic disorders: a systematic review with meta-analysis of the epidemiological evidence. *Environmental health : a global access science source* **14**: 46. doi: 10.1186/s12940-015-0036-5.
- Rasmussen, K.M., Catalano, P.M., and Yaktine, A.L. 2009. New guidelines for weight gain during pregnancy: what obstetrician/gynecologists should know. *Current opinion in obstetrics & gynecology* **21**(6): 521-526. doi: 10.1097/GCO.0b013e328332d24e.
- Rayfield, S., and Plugge, E. 2017. Systematic review and meta-analysis of the association between maternal smoking in pregnancy and childhood overweight and obesity. *Journal of epidemiology and community health* **71**(2): 162-173. doi: 10.1136/jech-2016-207376.
- Regnault, T.R., Gentili, S., Sarr, O., Toop, C.R., and Sloboda, D.M. 2013. Fructose, pregnancy and later life impacts. *Clinical and experimental pharmacology & physiology* **40**(11): 824-837. doi: 10.1111/1440-1681.12162.
- Reilly, J.J., Armstrong, J., Dorosty, A.R., Emmett, P.M., Ness, A., Rogers, I., et al. 2005. Early life risk factors for obesity in childhood: cohort study. *Bmj* **330**(7504): 1357. doi: 10.1136/bmj.38470.670903.E0.
- Riedel, C., Schonberger, K., Yang, S., Koshy, G., Chen, Y.C., Gopinath, B., et al. 2014. Parental smoking and childhood obesity: higher effect estimates for maternal smoking in pregnancy compared with paternal smoking--a meta-analysis. *Int J Epidemiol* **43**(5): 1593-1606. doi: 10.1093/ije/dyu150.
- Robinson, S.M., and Godfrey, K.M. 2008. Feeding practices in pregnancy and infancy: relationship with the development of overweight and obesity in childhood. *Int J Obes (Lond)* **32 Suppl 6**: S4-10. doi: 10.1038/ijo.2008.201.
- Rundle, A., Hoepner, L., Hassoun, A., Oberfield, S., Freyer, G., Holmes, D., et al. 2012. Association of childhood obesity with maternal exposure to ambient air polycyclic aromatic hydrocarbons during pregnancy. *Am J Epidemiol* **175**(11): 1163-1172. doi: 10.1093/aje/kwr455.
- Rutayisire, E., Huang, K., Liu, Y., and Tao, F. 2016. The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review. *BMC gastroenterology* **16**(1): 86. doi: 10.1186/s12876-016-0498-0.
- Schellong, K., Schulz, S., Harder, T., and Plagemann, A. 2012. Birth weight and long-term overweight risk: systematic review and a meta-analysis including 643,902 persons from 66 studies and 26 countries globally. *PLoS One* **7**(10): e47776. doi: 10.1371/journal.pone.0047776.

Schultz, M., Gottl, C., Young, R.J., Iwen, P., and Vanderhoof, J.A. 2004. Administration of oral probiotic bacteria to pregnant women causes temporary infantile colonization. *J Pediatr Gastroenterol Nutr* **38**(3): 293-297.

Sekirov, I., Russell, S.L., Antunes, L.C., and Finlay, B.B. 2010. Gut microbiota in health and disease. *Physiological reviews* **90**(3): 859-904. doi: 10.1152/physrev.00045.2009.

Sharp, G.C., Lawlor, D.A., Richmond, R.C., Fraser, A., Simpkin, A., Suderman, M., et al. 2015. Maternal pre-pregnancy BMI and gestational weight gain, offspring DNA methylation and later offspring adiposity: findings from the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol* **44**(4): 1288-1304. doi: 10.1093/ije/dyv042.

Silventoinen, K., Jelenkovic, A., Sund, R., Hur, Y.M., Yokoyama, Y., Honda, C., et al. 2016. Genetic and environmental effects on body mass index from infancy to the onset of adulthood: an individual-based pooled analysis of 45 twin cohorts participating in the COLlaborative project of Development of Anthropometrical measures in Twins (CODATwins) study. *The American journal of clinical nutrition* **104**(2): 371-379. doi: 10.3945/ajcn.116.130252.

Simmonds, M., Burch, J., Llewellyn, A., Griffiths, C., Yang, H., Owen, C., et al. 2015. The use of measures of obesity in childhood for predicting obesity and the development of obesity-related diseases in adulthood: a systematic review and meta-analysis. *Health technology assessment (Winchester, England)* **19**(43): 1-336. doi: 10.3310/hta19430.

Sloboda, D.M., Li, M., Patel, R., Clayton, Z.E., Yap, C., and Vickers, M.H. 2014. Early life exposure to fructose and offspring phenotype: implications for long term metabolic homeostasis. *J Obes* **2014**: 203474. doi: 10.1155/2014/203474.

Soeda, J., Mouralidarane, A., Cordero, P., Li, J., Nguyen, V., Carter, R., et al. 2016. Maternal obesity alters endoplasmic reticulum homeostasis in offspring pancreas. *Journal of physiology and biochemistry* **72**(2): 281-291. doi: 10.1007/s13105-016-0476-6.

Stratakis, N., Gielen, M., Chatzi, L., and Zeegers, M.P. 2014. Effect of maternal n-3 long-chain polyunsaturated fatty acid supplementation during pregnancy and/or lactation on adiposity in childhood: a systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Nutr* **68**(12): 1277-1287. doi: 10.1038/ejcn.2014.158.

Tanentsapf, I., Heitmann, B.L., and Adegboye, A.R. 2011. Systematic review of clinical trials on dietary interventions to prevent excessive weight gain during pregnancy among normal weight, overweight and obese women. *BMC Pregnancy Childbirth* **11**: 81. doi: 10.1186/1471-2393-11-81.

Tang-Peronard, J.L., Heitmann, B.L., Andersen, H.R., Steuerwald, U., Grandjean, P., Weihe, P., et al. 2014. Association between prenatal polychlorinated biphenyl exposure and obesity development at ages 5 and 7 y: a prospective cohort study of 656 children from the Faroe Islands. *The American journal of clinical nutrition* **99**(1): 5-13. doi: 10.3945/ajcn.113.066720.

Tate, E.B., Wood, W., Liao, Y., and Dunton, G.F. 2015. Do stressed mothers have heavier children? A meta-analysis on the relationship between maternal stress and child body mass index. *Obesity reviews : an official journal of the International Association for the Study of Obesity* **16**(5): 351-361. doi: 10.1111/obr.12262.

Tie, H.T., Xia, Y.Y., Zeng, Y.S., Zhang, Y., Dai, C.L., Guo, J.J., et al. 2014. Risk of childhood overweight or obesity associated with excessive weight gain during pregnancy: a meta-analysis. *Archives of gynecology and obstetrics* **289**(2): 247-257. doi: 10.1007/s00404-013-3053-z.

Tyrrell, J., Richmond, R.C., Palmer, T.M., Feenstra, B., Rangarajan, J., Metrustry, S., et al. 2016. Genetic Evidence for Causal Relationships Between Maternal Obesity-Related Traits and Birth Weight. *Jama* **315**(11): 1129-1140. doi: 10.1001/jama.2016.1975.

Vafeiadi, M., Georgiou, V., Chalkiadaki, G., Rantakokko, P., Kiviranta, H., Karachaliou, M., et al. 2015. Association of Prenatal Exposure to Persistent Organic Pollutants with Obesity and Cardiometabolic Traits in Early Childhood: The Rhea Mother-Child Cohort (Crete, Greece). *Environ Health Perspect* **123**(10): 1015-1021. doi: 10.1289/ehp.1409062.

Valvi, D., Mendez, M.A., Garcia-Esteban, R., Ballester, F., Ibarluzea, J., Goni, F., et al. 2014. Prenatal exposure to persistent organic pollutants and rapid weight gain and overweight in infancy. *Obesity (Silver Spring)* **22**(2): 488-496. doi: 10.1002/oby.20603.

Warrington, N.M., Howe, L.D., Paternoster, L., Kaakinen, M., Herrala, S., Huikari, V., et al. 2015. A genome-wide association study of body mass index across early life and childhood. *Int J Epidemiol* **44**(2): 700-712. doi: 10.1093/ije/dyv077.

Whitaker, R.C., Wright, J.A., Pepe, M.S., Seidel, K.D., and Dietz, W.H. 1997. Predicting obesity in young adulthood from childhood and parental obesity. *N Engl J Med* **337**(13): 869-873. doi: 10.1056/nejm199709253371301.

Woo Baidal, J.A., Locks, L.M., Cheng, E.R., Blake-Lamb, T.L., Perkins, M.E., and Taveras, E.M. 2016. Risk Factors for Childhood Obesity in the First 1,000 Days: A Systematic Review. *Am J Prev Med* **50**(6): 761-779. doi: 10.1016/j.amepre.2015.11.012.

Yan, J., Liu, L., Zhu, Y., Huang, G., and Wang, P.P. 2014. The association between breastfeeding and childhood obesity: a meta-analysis. *BMC Public Health* **14**: 1267. doi: 10.1186/1471-2458-14-1267.

Yu, Z., Han, S., Zhu, J., Sun, X., Ji, C., and Guo, X. 2013. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. *PLoS One* **8**(4): e61627. doi: 10.1371/journal.pone.0061627.

Yu, Z.B., Han, S.P., Zhu, G.Z., Zhu, C., Wang, X.J., Cao, X.G., et al. 2011. Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity* **12**(7): 525-542. doi: 10.1111/j.1467-789X.2011.00867.x.

Zheng, M., Lamb, K.E., Grimes, C., Laws, R., Bolton, K., Ong, K.K., et al. 2018. Rapid weight gain during infancy and subsequent adiposity: a systematic review and meta-analysis of evidence. *Obesity reviews : an official journal of the International Association for the Study of Obesity* **19**(3): 321-332. doi: 10.1111/obr.12632.

**Table 1. Summary of high-quality evidence for prenatal determinants of childhood obesity**

| <b>Factors</b>                         | <b>First author<br/>(ref.)</b>                  | <b>Publica-<br/>tion year</b> | <b>Study type</b>  | <b>Total<br/>number<br/>of<br/>studies</b> | <b>Age in<br/>outcome</b> | <b>Effect size</b>  |
|--|---|-------------------------------|--------------------|--|---------------------------|---|
| <b>Gene</b>                            | Horikoshi M<br>(Horikoshi et al.<br>2016)       | 2016                          | Meta-<br>analysis  | 60 loci                                    | 0 day                     | 15.1% (standard error = 0.9) of variance in birthweight could be decided by fetal genetic variation.  |
|  | Silventoinen K<br>(Silventoinen et<br>al. 2016) | 2016                          | Pooled<br>analysis | 45 twin<br>cohorts                         | 0 day                     | BMI variations explained by additive genetic factors increased from 0.42 in boys and 0.41 in girls at 4 years of age to 0.75 in both sexes at 19 years of age.    |
|  | Tyrrell, J<br>(Tyrrell et al.<br>2016)          | 2016                          | Meta-<br>analysis  | 18<br>studies                              | 0 day                     | A 1-SD genetically higher maternal BMI was associated with a 55 g (95%CI 17, 93 g) higher offspring birth weight.   |
| <b>Maternal<br/>pre-<br/>pregnancy</b> | Yu Z (Yu et al.<br>2013)                        | 2013                          | Meta-<br>analysis  | 4 studies                                  | 3 - 16<br>years           | Pre-pregnancy overweight/obesity increased the risk of offspring overweight (OR 1.95; 95% CI 1.77, 2.13); and obesity (OR 3.06; 95% CI 2.68, 3.49), respectively. |

|                                |  |      |                   |            |              |   |
|--------------------------------|--|------|-------------------|------------|--------------|---|
| <b>BMI</b>                     |  |      |                   |            |              |   |
|                                | Castillo-Laura H<br>(Castillo-Laura et al. 2015) | 2015 | Meta-analysis     | 8 studies  | 0 - 6 years  | Mean differences were 0.38kg (95% CI 0.26, 0.50) in fat mass, and 0.31 percentage (95% CI 0.19, 0.42) in percent body fat between infants born from overweight/obese women and those from normal pre-pregnancy BMI women, respectively. |
| <b>Gestational weight gain</b> | Mamun AA<br>(Mamun et al. 2014)                  | 2014 | Meta-analysis     | 12 studies | 2 - 42 years | Pregnant women with excessive GWG had an increased risk of obesity in the offspring (OR 1.40; 95% CI 1.23, 1.59), while women who had inadequate GWG had a 14% (OR 0.86; 95% CI 0.78, 0.94) reduction in future offspring obesity.      |
|                                | Tie HT<br>(Tie et al. 2014)                      | 2014 | Meta-analysis     | 15 studies | 2-18 years   | OR of excessive GWG and childhood overweight/obesity was 1.21 (95% CI 1.05,1.40).   |
|                                | Nehring I<br>(Nehring et al. 2013)               | 2013 | Meta-analysis     | 7 studies  | 2-20 years   | OR of excessive GWG and childhood overweight was 1.38 (95% CI 1.21, 1.57); and OR of inadequate GWG and childhood overweight was 0.91 (95% CI 0.85, 0.98).  |
|                                | Lau EY<br>(Lau et al. 2014)                      | 2014 | Systematic review | 23 studies | 2-19 years   | The association between GWG and later offspring BMI may be stronger during early- and mid-pregnancy than late pregnancy.  |
|                                | Castillo-Laura H                                 | 2015 | systematic        | 7 studies  | 0 - 6        | There were positive relationships between maternal GWG and fat  |

|                              |                                 |      |                   |            |              |   |
|------------------------------|---------------------------------|------|-------------------|------------|--------------|---|
|                              | (Castillo-Laura et al. 2015)    |      | review            |            | years        | mass, and between maternal GWG and percent body fat.  |
| <b>Diabetes in pregnancy</b> | Logan KM<br>(Logan et al. 2017) | 2017 | Meta-analysis     | 35 studies | 0 - 3 weeks  | Infants of maternal diabetes had higher fat mass (difference 83 g; 95% CI 49, 117), and percent body fat (difference 2.2%; 95% CI 1.1%, 3.2%) in infancy. Infants of mothers with GDM had higher fat mass (difference 62 g; 95% CI 29, 94), and percent body fat than infants of mothers without diabetes (difference 1.7%; 95% CI 0.7%, 2.8%). |
|                              | Kim SY<br>(Kim et al. 2011)     | 2011 | Systematic Review | 12 studies | 2 - 18 years | Crude odds ratios for the relationship between GDM and childhood overweight or obesity ranged from 0.7 to 6.3, but inconsistent evidence existed.   |
| <b>Caesarean section</b>     | Li HT<br>(Li et al. 2013)       | 2013 | Meta-analysis     | 9 Studies  | 0 - 25 years | Compared with those born vaginally, OR of overweight/obesity for offspring delivered by cesarean section was 1.33 (95% CI 1.19, 1.48); the OR was 1.32 (95% CI 1.15, 1.51) for children, 1.24 (95% CI 1.00, 1.54) for adolescents and 1.50 (95% CI 1.02, 2.20) for adults.  |
|                              | Kuhle S<br>(Kuhle et al. 2015)  | 2015 | Meta-analysis     | 28 studies | 2 - 18 years | Compared with those born vaginally, RR of childhood obesity delivered by cesarean section was 1.34 (95% CI 1.18–1.51).  |



|                         |  |      |                  |            |              |   |
|-------------------------|--|------|------------------|------------|--------------|---|
| <b>Maternal smoking</b> | Oken E<br>(Oken et al. 2008)             | 2008 | Meta-analysis    | 14 studies | 3 - 33 years | OR of maternal smoking and offspring overweight was 1.40 (95% CI 1.26, 1.55).   |
|                         | Rayfield S<br>(Rayfield and Plugge 2017) | 2017 | Meta-analysis    | 39 studies | 2 - 18 years | Maternal smoking in pregnancy increased the risk of childhood overweight (OR 1.37; 95% CI 1.28, 1.46) and childhood obesity (OR 1.55; 95% CI 1.40, 1.73).   |
|                         | Riedel C<br>(Riedel et al. 2014)         | 2014 | Meta-analysis    | 12 studies | 3 - 18 years | Maternal smoking during pregnancy increased the risk of offspring overweight (OR 1.33; 95% CI 1.23, 1.44) and obesity (OR 1.60; 95% CI 1.37, 1.88); paternal smoking increased the risk of offspring overweight (OR 1.07; 95% CI 1.00, 1.16), and obesity (OR 1.23; 95% CI 1.10, 1.38). |
| <b>Obesogens</b>        | Braun JM<br>(Braun 2017)                 | 2017 | Narrative review | -          | 0 - 21 years | Prenatal perfluoroalkyl substances (PFAS) exposure can be associated with reduced fetal growth, excess adiposity and risk of being overweight or obese, by disrupting hormone-mediated processes during critical periods of development.  |
|                         | Iszatt N<br>(Iszatt et al. 2015)         | 2015 | Pooled Analysis  | 12 studies | 2 years      | Prenatal p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) was associated with increased infant growth in weight-for-age z-score (per interquartile increase in exposure for an increase of 388 ng/g lipid, $\beta = 0.12$ ; 95% CI 0.03, 0.22).   |

|                                     |  |      |                   |            |                |  |
|-------------------------------------|--|------|-------------------|------------|----------------|--|
| <b>Maternal fatty acids</b>         | Hauner H<br>(Hauner et al. 2013)       | 2013 | Systematic Review | 6 Studies  | 1 - 19 years   | Little evidence to support dietary intervention of fatty acids during pregnancy to modify fat composition for childhood obesity.   |
|                                     | Stratakis N<br>(Stratakis et al. 2014) | 2014 | Meta-analysis     | 9 Studies  | 1.5 - 19 years | No effect of maternal n-3 long-chain polyunsaturated fatty acid supplementation during pregnancy and/or lactation on BMI in preschool (difference 0.07; 95% CI, 0.22, 0.36, $P = 0.65$ ) and school-aged children (difference 0.12; 95% CI 0.06, 0.30, $P = 0.20$ ). |
| <b>Maternal psychosocial stress</b> | Tate EB<br>(Tate et al. 2015)          | 2015 | Meta-analysis     | 17 studies | 0 - 13 years   | Levels of prenatal psychological stress experienced were associated with childhood BMI. The overall mean differences of obesity risk were 0.20 (95% CI 0.06, 0.34) in cross-sectional studies and 0.18 (95% CI 0.00, 0.351) in longitudinal studies.                 |

BMI, body mass index; CI, confidence interval; RR, risk ratio; OR, odds ratio; GWG, gestational weight gain; GDM, gestational diabetes mellitus