DOI 10.1002/mnfr.201500289 *Mol. Nutr. Food Res.* 2016, *60*, 8–17

REVIEW

Maternal obesity in females born small: Pregnancy complications and offspring disease risk

Dayana Mahizir[1], Jessica F. Briffa[1], Deanne H. Hryciw[1], Glenn D. Wadley[2], Karen M. Moritz[3] and Mary E. Wlodek[1]

[1] Department of Physiology, The University of Melbourne, Parkville, Victoria, Australia
[2] Centre for Physical Activity and Nutrition Research, School of Exercise and Nutrition Sciences, Deakin University, Burwood, Victoria, Australia
[3] School of Biomedical Sciences, University of Queensland, St. Lucia, Queensland, Australia

Received: April 14, 2015
Revised: July 5, 2015
Accepted: July 7, 2015

Obesity is a major public health crisis, with 1.6 billion adults worldwide being classified as overweight or obese in 2014. Therefore, it is not surprising that the number of women who are overweight or obese at the time of conception is increasing. Obesity during pregnancy is associated with the development of gestational diabetes and preeclampsia. The developmental origins of health and disease hypothesis proposes that perturbations during critical stages of development can result in adverse fetal changes that leads to an increased risk of developing diseases in adulthood. Of particular concern, children born to obese mothers are at a greater risk of developing cardiometabolic disease. One subset of the population who are predisposed to developing obesity are children born small for gestational age, which occurs in 10% of pregnancies worldwide. Epidemiological studies report that these growth-restricted children have an increased susceptibility to type 2 diabetes, obesity, and hypertension. Importantly during pregnancy, growth-restricted females have a higher risk of developing cardiometabolic disease, indicating that they may have an exacerbated phenotype if they are also overweight or obese. Thus, the development of early pregnancy interventions targeted to obese mothers may prevent their children from developing cardiometabolic disease in adulthood.

Keywords:
Developmental programing / Fetal growth restriction / Insulin resistance / Maternal pregnancy / Obesity

1 Introduction

Obesity is clinically defined as having a BMI over 30 (World Health Organization (WHO) 2015; http://www.who.int/mediacentre/factsheets/fs311/en/), and is associated with an increased risk of developing a number of comorbidities, including cardiovascular and metabolic diseases and nephropathy [1]. A recent report by McKinsey Global Institute stated that obesity is considered one of the top three global social burdens generated by human beings, along with smoking and armed violence, and it is estimated that $2.0 trillion USD is spent worldwide annually as a result of obesity (McKinsey Global Institute 2014; http://www.mckinsey.com/insights/economic_studies/how_the_world_could_better_fight_obesity). Since 1980, obesity rates worldwide have more than doubled with 2.1 billion people, or nearly 30% of the global population, classified as being obese or overweight in 2013 [2]. Of major concern, there were 42 million children under 5 years of age who are overweight or obese in 2013 according to the WHO (2015).

The dramatic increase in the prevalence of obesity in recent years is suggested to be caused by a poor early life environment, which can have long-term effects on the susceptibility of the developing offspring to develop a wide range of adverse conditions in adulthood. Indeed, there has been a plethora of epidemiological and experimental evidence that strongly suggest that alterations in the in utero environment, due to maternal nutrition, including maternal obesity and maternal undernutrition, programs the developing offspring to develop cardiovascular and metabolic disease later in life [3, 4]. The disturbances during critical stages of development can result in adverse changes in fetal physiology, which predispose the fetus to a number of diseases in adulthood. In fact, other studies relate insults during critical periods of

Correspondence: Mary E. Wlodek
E-mail: m.wlodek@unimelb.edu.au

Abbreviations: **NPY**, neuropeptide Y; **POMC**, proopiomelanocortin

development to adverse conditions later in life, such as type 2 diabetes [4, 5], hypertension [6, 7], and obesity [8, 9]. The fetus often responds to the poor conditions in an adverse intrauterine environment by undergoing physiological and metabolic adaptations in order to protect the most vital organs, such as brain, at the detriment of other organs [10]. This "thrifty phenotypes hypothesis" suggests that when the postnatal nutritional environment is similar, the individuals would then be able to endure the poor condition, but the adaptations become detrimental when the postnatal nutrition is different than the in utero environment [10, 11].

2 Obesity in pregnancy

Pregnancy is the greatest physiological challenge facing women that results in alterations in maternal physiology and metabolism to assist in fetal growth and development, which is modulated by a number of key molecules [12]. For example, glucose, the primary nutrient crossing the placenta, is important for fetal and placental growth [12, 13]. During pregnancy, glucose homeostasis in the mother is altered so that there is a progressive increase in insulin resistance and gluconeogenetic activity to sustain glucose transfer to the fetus [14]. Lipid metabolism is also altered in pregnancy with a significant increase in plasma cholesterol and triglyceride concentrations due to enhanced lipolytic activity and reduced lipoprotein lipase activity of adipose tissue during late gestation [15, 16]. During the first and second trimester, the mother is in an anabolic state whereby an increase in lipogenesis activity and adipose tissue lipoprotein lipase activity causes the mothers fat depots to accumulate [12]. The mother then shifts into a catabolic state during late pregnancy when fetal growth accelerates [17].

In an obese mother, the pregnancy adaptations differ from what occurs in healthy pregnant women. For example, glucose metabolism is significantly altered with an increase in peripheral and hepatic insulin resistance during the first trimester of pregnancy compared to normal weight pregnant women [18]. Therefore, is not surprising that the incidence of gestational diabetes is higher in overweight or obese pregnant women with a two- to tenfold increase [19–23]. In fact, obese women who were not diagnosed with gestational diabetes or impaired glucose tolerance have higher glucose profiles than normal weight women both during early and late pregnancy, despite consuming a controlled diet [24]. Similarly, women who had a higher gestational weight gain throughout the first 24 wks of pregnancy have a greater risk of developing gestational diabetes [25] and the risk was more pronounced when the women were obese [26]. Clearly, there is a linear association between BMI and the incidence of gestational diabetes. The mechanisms underlying this adverse pregnancy outcome are poorly understood. However, abdominal fat accumulation in obese women during pregnancy is likely to be associated with an increase in inflammatory cytokine production, leading to insulin resistance [27].

Obesity is a chronic low-grade inflammatory condition that is characterized by increased adipocyte mass, an increase in fasting whole body free fatty acids, and glycerol released from adipocytes [28]. White adipose tissue produces several proinflammatory cytokines, such as TNF-α and IL-6, which are increased in obesity [29]. Importantly, the placenta also produces these inflammatory cytokines, with the exception of adiponectin [30, 31]. Similar to the upregulation of inflammatory cytokine expression in obese adipose tissue, there is a two- to threefold increase in proinflammatory cytokine expression (IL-1, TNF-α, and IL-6) in the obese placenta, which is likely due to increased macrophage infiltration compared to a healthy pregnant women [32]. Likewise, the plasma concentrations of C-reactive protein, IL-6, and leptin were also increased in pregnant obese women compared to normal weight women [27, 32]. Obese women who were diagnosed with gestational diabetes were reported to have low serum adiponectin, a marker for increased insulin sensitivity, at 24–28 wk of pregnancy as compared to women with obesity alone [33]. Thus, these studies demonstrate that maternal obesity is associated with increased inflammatory mediator expression in the maternal plasma and placenta, which may contribute to an inflammatory in utero environment for the developing fetus.

3 The effects of maternal obesity on offspring health

It is well established that maternal obesity is associated with increased fetal growth, which can lead to offspring being born macrosomic [34]. However, recent findings suggest that offspring born to obese mother can also be small for gestational age or born with a normal birth weight [35, 36]. Of particular note, being small or large for gestational age due to maternal obesity predispose the offspring to obesity in adulthood [9]. Several animal studies have investigated the relationship between maternal obesity and the development of obesity in the offspring [37–39]. In rats, exposure to maternal obesity during pregnancy and lactation increased the risk of obesity later in life [37, 38]. The risk of obesity was further exacerbated when the offspring consumed a high fat diet postweaning [37, 40]. These clearly indicate that maternal obesity increased the obesity risk in their offspring. There are a number of mechanisms that may explain the programing effects of maternal obesity on offspring obesity risk including programing of appetite dysregulation and altered adipogenesis.

A study reported that the offspring of mice that consumed a high fat diet throughout pregnancy and lactation were hyperphagic from 4 to 6 wk of age before they developed abdominal obesity at 3 months [39]. Similarly, offspring of rats exposed to a junk food diet during both pregnancy and lactation displayed an increased preference for fatty, sugary, and salty foods when compared to offspring exposed to a control diet [37]. Programed changes in the offspring

of obese mothers may be a consequence of changes in hypothalamic functioning, which has an important role in the regulation of appetite. Appetite is primarily regulated by the hypothalamic arcuate nucleus and is composed of two neuron populations that either express the appetite stimulator neuropeptide Y (NPY) or the appetite inhibitor pro-opiomelanocortin (POMC) [41]. These neurons project into the paraventricular nucleus where they exert their effect on appetite regulation [41]. Importantly, the development of appetite regulation occurs during late gestation and perturbations during these critical periods may lead to a dysregulation in the expression of hypothalamic neuropeptides, increasing the risk of obesity in adulthood [41]. In rats, offspring of dams exposed to a cafeteria diet during pregnancy and lactation have increased hypothalamic NPY signaling [42]. Additionally, offspring born from genetically obese Zucker rats had reduced expression of POMC and lower α-melanocyte stimulating hormone, a cleaved product of POMC [43]. It is suggested that the changes in these neuronal pathways may be due to increased circulating leptin and insulin in the obese state, which are known to play a major role in regulating appetite by stimulating POMC and inhibiting NPY hypothalamic neurons [44, 45]. Therefore, it is postulated that exposure to maternal obesity causes alterations in hypothalamic regulation of appetite in the offspring leading to the development of hyperphagia.

Maternal obesity is also associated with dysfunction in offspring adipose tissue development. Offspring of rat dams fed a "junk food" diet during gestation and lactation demonstrated adipocyte hypertrophy, independent of hyperplasia, with increased expression of adipogenic factor peroxisome proliferator-activated receptor gamma, insulin-like growth factor 1, insulin receptor substrate 1, and vascular endothelial growth factor A mRNA expression at 10 wk of age, indicative of altered adipocyte proliferation [46]. Similarly, maternal overnutrition during late gestation in sheep is also associated with increased expression of genes, which regulate adipogenesis and lipogenesis in fetal perirenal adipose tissue, including lipoprotein lipase, adiponectin, leptin, and peroxisome proliferator-activated receptor gamma [47]. These findings suggest that alterations in adipose gene expression may be one of the underlying mechanisms that increase adiposity in offspring that are exposed to maternal overnutrition.

In addition to increasing the risk of offspring obesity, maternal obesity and overnutrition also program metabolic dysfunction in their offspring. Limited human studies have examined the link between maternal obesity, offspring insulin resistance, and other adverse metabolic outcomes. For instance, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study reported that an increase in maternal BMI is linked with fetal hyperinsulinemia, which is independent of maternal glycaemia [48]. Importantly, there is evidence that demonstrates that babies of obese mothers develop insulin resistance in utero, indicating that maternal obesity is an important predictor of metabolic disease in their offspring [49]. The effect maternal obesity has on insulin sensitivity then persists into later life with children of overweight women having an increased risk of developing insulin resistance by 11 years of age [4], and in early adulthood (early 20s) [50]. Therefore, these findings support the association of maternal obesity and altered glucose–insulin homeostasis in the offspring.

Indeed, in animal studies, maternal obesity or overnutrition during both pregnancy and lactation is linked to increased insulin and glucose concentrations in the offspring and these features were exacerbated when the offspring consumed a high-fat diet postweaning [39, 46, 51–53]. Studies suggest that alteration in glucose–insulin homeostasis in offspring of obese mothers is likely due to β-cell failure [54–57]. Evidence in rat studies demonstrated consumption a high-fat diet (40% calories from fat) during pregnancy and lactation caused hyperglycemia and insulin resistance with compromised β-cell development and function in the offspring [54, 55]. Additionally, offspring of obese mice develop insulin resistance at 3 months of age, but by 6 months of age male offspring developed frank diabetes with reduced plasma insulin and pancreatic insulin content, indicative of β-cell exhaustion [39]. Other animal studies recorded similar observations, suggesting that there is an age-related decline in β-cell function in offspring of obese mothers that leads to altered glucose and insulin homeostasis [56, 57]. In sheep, maternal obesity is linked to an increased fetal pancreatic weight and an increased number of insulin-positive cells per unit area, which is indicative of accelerated β-cell maturation [58]. A further study showed that offspring of high-fat dams had reduced β-cell numbers and this was associated with an increased in β-cell apoptotic rate [59]. Therefore, these changes may predispose the offspring to a premature loss of β-cell function which would subsequently lead to elevated risk of metabolic disease in adulthood.

Taken together, these findings suggest that maternal obesity or overnutrition during pregnancy have an adverse effect on offspring metabolic outcomes [60]. Thus, further studies are required to understand the underlying mechanisms that predispose the offspring of obese mother to metabolic diseases and whether these adverse phenotypes can be modified by lifestyle interventions.

4 Intrauterine growth restriction

Obesity is a multifactorial disease, with a number of risk factors associated with its development. Exposure to a perturbations in utero, such as maternal malnutrition and placental insufficiency, program an increased risk of developing obesity in later life [61]. Intrauterine growth restriction affects 10% of pregnancies worldwide and is characterized by a term birth weight of less than 2.5 kg [62]. Growth restriction can be caused by genetic factors and maternal stressors, such as maternal smoking, maternal malnutrition, and placental dysfunction [63]. In Western societies uteroplacental insufficiency is the major cause of growth restriction [64–66],

whereas maternal malnutrition is the main cause of babies born small in developing countries [67,68]. Previous epidemiological studies have demonstrated an association between being born small and an increased risk of developing type 2 diabetes, obesity, and hypertension [5, 6, 69]. From these findings the importance of maternal nutrition and its effect on birth weight and subsequent adult diseases was addressed in human studies of famine exposure, particularly the Dutch Hunger Winter of 1944–1945 [70, 71]. The Dutch Hunger Winter study found that growth restriction due to famine exposure in utero is linked to glucose intolerance and abdominal obesity in adults [70, 72]. In contrast, the findings from famine exposure during the Leningrad siege (1941–1944) did not show any association between birth weight and metabolic disease risk [73]. The inconsistency between these findings is likely due to the different nutritional environments during the postnatal period in both studies. Following the Dutch Hunger Winter, the food supply was restored to normal levels in a short period of time, where they were exposed to normal nutrition during their postnatal life [70, 73]. Conversely in Leningrad, the children were exposed to poor nutritional environment in utero and in their early postnatal years [73]. These findings suggest that a mismatch in nutritional environment between the intrauterine and postnatal period may influence the outcomes of growth-restricted babies in adulthood.

Altered postnatal growth can also influence the disease outcomes of growth-restricted babies in adulthood. Growth-restricted babies often experience catch up growth in the first 6 to 12 months of age and to as late as 2 years after birth when the postnatal nutritional environment is improved [74]. They will accelerate their growth trajectory to match the growth of normal weight babies to compensate for their low birth weight. Previous studies have reported that children born small for gestational age, who have a high childhood fat mass, have an increased risk of developing diabetes in later life [75, 76] and present with insulin resistance at 3 years [77]. Another study in a cohort from Helsinki demonstrated that growth-restricted individuals have an exacerbated risk of type 2 diabetes when catch up growth in early postnatal life (6 months of age) is combined with accelerated weight gain during adolescence [78]. These studies suggest that accelerated catch up growth during postnatal life is an additional independent risk factor to disease development in growth-restricted individuals. Therefore, a combination of adverse pre- and postnatal environment can lead to an exacerbation of the programed diseases in these individuals.

Animal models have been extensively used to identify the underlying mechanisms that associate intrauterine growth restriction and the risk of metabolic dysfunction in adulthood. Indeed, many studies using a wide range of animal species, including sheep, rodents and guinea pig, have demonstrated the link between intrauterine growth restriction and metabolic disease [79]. The majority of animal models investigating intrauterine growth restriction have utilized dietary interventions to induce maternal undernutrition [80, 81] and surgical interventions to induce uteroplacental insufficiency [82]. In Wistar rat, exposure to 50% caloric restriction in the last trimester of pregnancy resulted in a 16% reduction in birth weight compared to control offspring [83, 84]. However, the effect caloric restriction has on adiposity is contradictory with this study identifying no change [83, 84], whereas another study identified increased adiposity, which is consistent with the hyperleptinemia observed in these animals [85]. Despite these differences in adiposity, caloric restriction results in catch up growth [86] and alters β-cell morphology and function [83, 84]. Specifically, caloric restriction and low-protein diets (8% protein) reduce β-cell mass [83, 87–89] and insulin content [83, 87]. Interestingly, when these offspring were exposed to a normal diet postnatally, the islet morphology improved, indicating that the in utero environment influences fetal islet development [88, 89]. However, if protein restriction was extended during weaning, these modifications were irreversible [88,89]. Studies in male rat offspring of low-protein diet dams demonstrated an age-dependent loss in glucose tolerance. Specifically, they had improved glucose tolerance and reduced plasma insulin concentrations in early life (6 wk to 3 months), which is indicative of enhanced insulin sensitivity [90]. Nevertheless, when they reached 15 months of age, glucose intolerance was evident [91] and by 17 months of age they developed frank diabetes and insulin resistance [92].

As mentioned previously in developed countries, placental insufficiency is the major cause of intrauterine growth restriction and low birth weight [64–66]. Wigglesworth was the first to describe the model of uteroplacental insufficiency in rats by ligating the uterine vessels during late gestation, which reduced uteroplacental nutrient and oxygen perfusion and thus compromises fetal growth and development [82]. This rat model is equivalent to the degree of birth weight reduction observed in humans in developed countries (10–15% reduction in birth weight), where developmental insults are most apparent during late gestation [93]. Uteroplacental insufficiency surgery in Sprague Dawley rats between embryonic days 16 and 19 (E16-19; term = 22 days) resulted in low birth weight offspring (10–15%) [64, 94, 95]. These offspring had reductions in β-cell mass at birth [95, 96], with a similar decrease in pancreatic insulin content [95], however, glucose tolerance was normal at 3 months of age [95]. In contrast, a study by Simmons et al. reported that male growth-restricted Sprague Dawley rats had normal β-cell mass, islet size, and pancreatic weight at 1 and 7 wk of age [64]. However, at 15 wk of age, these rats had reduced β-cell mass and decreased pancreatic insulin content as well as a reduced insulin response to glucose, and at 26 wk these offspring were diabetic and obese [64]. Additionally, other uteroplacental insufficiency studies recorded fasting hyperglycemia, early onset insulin resistance, obesity, and impaired glucose tolerance in the growth-restricted Sprague Dawley rats [64, 65, 97–100]. Findings from our laboratory reported that male Wistar Kyoto (WKY) rats that were exposed to uteroplacental insufficiency develop impaired glucose tolerance and were

hyperinsulinemic at 6 month of age, which was associated with a 40–45% reduction in β-cell mass [101–104]. Interestingly, growth-restricted female rats exhibited normal glucose tolerance regardless of reductions in basal insulin concentrations and pancreatic β-cell mass [101, 105]. Findings from these studies clearly suggest that there are sex-specific differences where growth-restricted males are more severely affected than females. Thus, "second hits," such as obesity or pregnancy, may exacerbate the adverse metabolic phenotype in growth-restricted females.

4.1 Growth restriction and obesity

Epidemiological studies and animal models link a low birth weight to an increased risk of adult obesity and metabolic syndrome [106, 107]. Early epidemiologic studies demonstrated that growth-restricted babies that experienced accelerated catch up growth have a higher risk of obesity and metabolic syndrome compared to infants that are born small and remain small throughout their life [108, 109]. Importantly, growth-restricted infants with catch up growth during their early postnatal life had reduced lean body mass and elevated abdominal fat [110, 111]. This finding is similar to what is reported in infants with a normal birth weight that exhibit rapid weight gain in the first 2 years of life [112]. Of particular concern, the Dutch Hunger Winter study reported that only women who were exposed to famine in early gestation had increased in body weight, BMI, and waist circumference in adulthood [72]. Likewise, girls aged between 14 and 16 years who were born small had increased central adiposity compared to growth-restricted males [113]. These findings indicate that growth-restricted females are at higher risk of abdominal obesity which is associated with an increased risk of insulin resistance and glucose intolerance.

4.2 Growth restriction and pregnancy

In females that were born growth-restricted, pregnancy may exacerbate their risk of cardiovascular and metabolic disease due to an increase in both maternal and fetal demands. Indeed, epidemiological studies associate a low birth weight with a higher risk of developing preeclampsia during later pregnancy [114, 115]. Furthermore, women born with a low birth weight were also more susceptible to gestational diabetes during pregnancy compared to women that were born of normal weight [116]. A study in female rats born small also identified a higher risk of developing gestational diabetes in pregnancy as well as an increased risk of their offspring developing an altered metabolic phenotype [94]. Likewise, we have previously demonstrated that growth-restricted female rats during late pregnancy develop glucose intolerance, despite a normal plasma insulin response [105]. Given that maternal obesity has adverse effects on glucose homeostasis during pregnancy, it is likely that the metabolic dysfunction in pregnant females who were born growth-restricted will be exacerbated if they consume a high-fat diet. Currently this association has not been investigated, thus future studies should examine this interaction.

So far, most of the developmental programing studies are largely descriptive and there are very limited molecular investigations have been performed in this area. Therefore, additional molecular studies are required to identify the underlying mechanisms that may explain the link of obesity in growth-restricted mothers to their pregnancy outcomes as well as their offspring development.

5 Potential intervention

There has been much interest in the development of lifestyle interventions targeting overweight and obese pregnant women. Of particular interest, epidemiological studies demonstrated that exercise in overweight and obese women prevented them from developing gestational diabetes as well as delivering macrosomic babies [117]. Moderate exercise during pregnancy improved glucose tolerance [118] and reduced fasting insulin [119] in obese pregnant women; thus, lowering their risk for gestational diabetes. Likewise, moderate to vigorous exercise in early pregnancy also improved insulin response and sensitivity, as well as reducing plasma triglyceride concentration in overweight and obese pregnant women [120]. However, there are studies that failed to associate the beneficial effects of exercise with a reduced risk of adverse pregnancy outcomes in overweight and obese women [121, 122]. Lack of consistent evidence regarding the benefits of exercise in pregnant obese or overweight women suggests that interventions during pregnancy alone may not be enough to ameliorate the adverse effect obesity has on the mother and her children. Therefore, an exercise intervention before and during pregnancy may be more beneficial. Indeed, in nonobese pregnant women who were involved in exercise training 1 year before pregnancy had a reduced risk of developing gestational diabetes [123–125], and the effect was greater in women who exercised before and during pregnancy [125]. These findings propose that these lifestyle interventions are more beneficial if they are performed before the reproductive years.

Similarly, in animal studies, maternal exercise reduced the metabolic risk caused by maternal obesity in both the mother and offspring [126, 127]. A recent study on rats reported that voluntary wheel running before and during pregnancy prevented the increase in plasma insulin and glucose, concentrations insulin resistance (HOMA-IR), and plasma triglyceride content during lactation in obese dams [126]. Additionally, voluntary exercise before and during pregnancy reduced glucose and insulin concentrations in male offspring (postnatal day 19) of obese rat mothers [128] and prevented glucose intolerance induced by maternal obesity in female offspring (24 wk) of C57BL/6 mice [128]. Of particular concern, most of the rodent studies investigating the effect of

exercise intervention in maternal obesity utilized a poorly controlled voluntary wheel running as the exercise intervention. Therefore, a well-controlled interventional animal study using a motorized treadmill exercise is required as precise exercise intensity and duration can be controlled.

6 Conclusions

There has been a significant increase in the number of overweight or obese pregnant women in the past two decades. Of particular concern, maternal obesity does not only affect the mother, but the offspring are programed to develop obesity and metabolic disease later in life. Studies suggest that the mechanisms contributing to this is due to appetite dysregulation and enhanced adipogenesis in the offspring. Being born small for gestational age is one of the risk factor for developing obesity. As being born small is associated with increased risk of cardiovascular and metabolic disease during pregnancy, it is suggested that obesity during pregnancy may exacerbate the risk of these diseases. However, there are limited studies investigating the effect of maternal obesity in growth-restricted mothers and the subsequent effects in their offspring. Therefore, it is critical to identify the underlying mechanisms that link obesity in growth-restricted mothers to the development of metabolic diseases in their offspring. This will be fundamental to future strategies for the prevention and therapy of obesity.

The authors have declared no conflicts of interest.

7 References

[1] Eckel, R. H., Grundy, S. M., Zimmet, P. Z., The metabolic syndrome. *Lancet* 2005, *365*, 1415–1428.

[2] Ng, M., Fleming, T., Robinson, M., Thomson, B. et al., 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* 2014, *384*, 766–781.

[3] Barker, D. J. P., The developmental origins of well-being. *Philos. Trans. R. Soc. Lond.* 2004, *359*, 1359–1366.

[4] Boney, C. M., Verma, A., Tucker, R., Vohr, B. R., Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics* 2005, *115*, 290–296.

[5] Hales, C. N., Barker, D. J., Clark, P. M., Cox, L. J. et al., Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991, *303*, 1019–1022.

[6] Barker, D. J. P., Osmond, C., Golding, J., Kuh, D. et al., Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 1989, *298*, 564–567.

[7] West, N. A., Crume, T. L., Maligie, M. A., Dabelea, D., Cardiovascular risk factors in children exposed to maternal diabetes in utero. *Diabetologia* 2011, *54*, 504–507.

[8] Law, C. M., Barker, D. J. P., Osmond, C., Fall, C. H. D. et al., Early growth and abdominal fatness in adult life. *Commun. Health* 1992, *46*, 184–186.

[9] Drake, A. J., Reynolds, R. M., Impact of maternal obesity on offspring obesity and cardiometabolic disease risk. *Reproduction* 2010, *140*, 387–398.

[10] Hales, C. N., Barker, D. J. P., Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 1992, *35*, 595–601.

[11] Morris, M., Early life influences on obesity risk: maternal overnutrition and programming of obesity. *Expert Rev. Endocrinol. Metab.* 2009, *4*, 625–637.

[12] Herrera, E., Metabolic adaptations in pregnancy and their implications for the availability of substrates to the fetus. *Eur. J Clin Nutr.* 2000, *54*, S47–S51.

[13] Nolan, C. J., Proietto, J., The feto-placental glucose steal phenomenon is a major cause of maternal metabolic adaptation during late pregnancy in the rat. *Diabetologia* 1994, *37*, 976–984.

[14] Herrera, E., Knopp, R. H., Freinkel, N., Carbohydrate metabolism in pregnancy. VI. Plasma fuels, insulin, liver composition, gluconeogenesis, and nitrogen metabolism during late gestation in the fed and fasted rat. *J. Clin. Invest.* 1969, *48*, 2260–2272.

[15] Merzouk, H., Meghelli-Bouchenak, M., Loukidi, B., Prost, J. et al., Impaired serum lipids and lipoproteins in fetal macrosomia related to maternal obesity. *Biol. Neonate* 2000, *77*, 17–24.

[16] Knopp, R. H., Herrera, E., Freinkel, N., Carbohydrate metabolism in pregnancy. 8. Metabolism of adipose tissue isolated from fed and fasted pregnant rats during late gestation. *J. Clin. Invest.* 1970, *49*, 1438–1446.

[17] Lopez-Luna, P., Munoz, T., Herrera, E., Body fat in pregnant rats at mid- and late-gestation. *Life Sci.* 1986, *39*, 1389–1393.

[18] Catalano, P. M., Ehrenberg, H. M., The short- and long-term implications of maternal obesity on the mother and her offspring. *BJOG*. 2006, *113*, 1126–1133.

[19] Sebire, N. J., Jolly, M., Harris, J. P., Wadsworth, J. et al., Maternal obesity and pregnancy outcome: a study of 287213 pregnancies in London. *Int. J. Obes. Relat. Metab. Disord.* 2001, *25*, 1175–1182.

[20] Kumari, A. S., Pregnancy outcome in women with morbid obesity. *Int. J. Gynaecol. Obstet.* 2001, *73*, 101–107.

[21] Bianco, A. T., Smilen, S. W., Davis, Y., Lopez, S. et al., Pregnancy outcome and weight gain recommendations for the morbidly obese woman. *Obstet. Gynecol.* 1998, *91*, 97–102.

[22] Cunningham, C. E., Teale, G. R., A profile of body mass index in a large rural Victorian obstetric cohort. *Med. J. Aust.* 2013, *198*, 39–42.

[23] Ramachenderan, J., Bradford, J., McLean, M., Maternal obesity and pregnancy complications: a review. *Aust. N. Z. J. Obstet. Gynaecol.* 2008, *48*, 228–235.

[24] Harmon, K. A., Gerard, L., Jensen, D. R., Kealey, E. H. et al., Continuous glucose profiles in obese and normal-weight pregnant women on a controlled diet: metabolic determinants of fetal growth. *Diabetes Care* 2011, *34*, 2198–2204.

[25] Gibson, K. S., Waters, T. P., Catalano, P. M., Maternal weight gain in women who develop gestational diabetes mellitus. *Obstet. Gynecol.* 2012, *119*, 560–565.

[26] Cisse, O., Fajardy, I., Dickes-Coopman, A., Moitrot, E. et al., Mild gestational hyperglycemia in rat induces fetal overgrowth and modulates placental growth factors and nutrient transporters expression. *Plos One* 2013, *8*, e64251.

[27] Ramsay, J. E., Ferrell, W. R., Crawford, L., Wallace, A. M. et al., Maternal obesity is associated with dysregulation of metabolic, vascular, and inflammatory pathways. *J. Clin. Endocrinol. Metab.* 2002, *87*, 4231–4237.

[28] Desai, M., Babu, J., Ross, M., Programmed metabolic syndrome: Prenatal undernutrition and post-weaning overnutrition. *Am. J. Physiol.* 2007, *293*, R2306–R2314.

[29] Shulman, G. I., Cellular mechanisms of insulin resistance. *J. Clin. Invest.* 2000, *106*, 171–176.

[30] Radaelli, T., Varastehpour, A., Catalano, P., Hauguel-de, M. S., Gestational diabetes induces placental genes for chronic stress and inflammatory pathways. *Diabetes* 2003, *52*, 2951–2958.

[31] Hauguel-de, M. S., Guerre-Millo, M., The placenta cytokine network and inflammatory signals. *Placenta* 2006, *27*, 794–798.

[32] Challier, J. C., Basu, S., Bintein, T., Minium, J. et al., Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta. *Placenta* 2008, *29*, 274–281.

[33] Hedderson, M. M., Darbinian, J., Havel, P. J., Quesenberry, C. P. et al., Low prepregnancy adiponectin concentrations are associated with a marked increase in risk for development of gestational diabetes mellitus. *Diabetes Care* 2013, *36*, 3930–3937.

[34] Ehrenberg, H. M., Mercer, B. M., Catalano, P. M., The influence of obesity and diabetes on the prevalence of macrosomia. *Am. J. Obstet. Gynecol.* 2004, *191*, 964–968.

[35] McIntyre, H. D., Gibbons, K. S., Flenady, V. J., Callaway, L. K., Overweight and obesity in Australian mothers: epidemic or endemic? *Med. J. Aust.* 2012, *196*, 184–188.

[36] Anderson, N. H., Sadler, L. C., Stewart, A. W., Fyfe, E. M. et al., Independent risk factors for infants who are small for gestational age by customised birthweight centiles in a multi-ethnic New Zealand population. *Aust. N. Z. J. Obstet. Gynaecol.* 2013, *53*, 136–142.

[37] Bayol, S. A., Farrington, S. J., Stickland, N. C., A maternal 'junk food' diet in pregnancy and lactation promotes an exacerbated taste for 'junk food' and a greater propensity for obesity in rat offspring. *Br. J. Nutr.* 2007, *98*, 843–851.

[38] Rajia, S., Chen, H., Morris, M. J., Maternal overnutrition impacts offspring adiposity and brain appetite markers—modulation by postweaning diet. *J. Neuroendocrinol.* 2010, *22*, 905–914.

[39] Samuelsson, A. M., Matthews, P. A., Argenton, M., Christie, M. R. et al., Diet-induced obesity in female mice leads to offspring hyperphagia, adiposity, hypertension, and insulin resistance: a novel murine model of developmental programming. *Hypertension* 2008, *51*, 383–392.

[40] Chen, H., Simar, D., Lambert, K., Mercier, J. et al., Maternal and postnatal overnutrition differentially impact appetite regulators and fuel metabolism. *Endocrinology* 2008, *149*, 5348–5356.

[41] Ross, M. G., Desai, M., Developmental programming of appetite/satiety. *Ann. Nutr. Metab.* 2014, *64*, 36–44.

[42] Chen, H., Simar, D., Morris, M. J., Hypothalamic neuroendocrine circuitry is programmed by maternal obesity: interaction with postnatal nutritional environment. *Plos One* 2009, *4*, 1–10.

[43] Kim, E. M., O'Hare, E., Grace, M. K., Welch, C. C. et al., ARC POMC mRNA and PVN alpha-MSH are lower in obese relative to lean Zucker rats. *Brain Res.* 2000, *862*, 11–16.

[44] Briffa, J. F., McAinch, A. J., Romano, T., Wlodek, M. E. et al., Leptin in pregnancy and development: a contributor to adulthood disease? *Am. J. Physiol.* 2015, *308*, E335–E350.

[45] Varela, L., Horvath, T. L., Leptin and insulin pathways in POMC and AgRP neurons that modulate energy balance and glucose homeostasis. *EMBO Rep.* 2012, *13*, 1079–1086.

[46] Bayol, S. A., Simbi, B. H., Bertrand, J. A., Stickland, N. C., Offspring from mothers fed a 'junk food' diet in pregnancy and lactation exhibit exacerbated adiposity that is more pronounced in females. *J. Physiol.* 2008, *586*, 3219–3230.

[47] Muhlhausler, B. S., Duffield, J. A., McMillen, I. C., Increased maternal nutrition stimulates peroxisome proliferator activated receptor-gamma, adiponectin, and leptin messenger ribonucleic acid expression in adipose tissue before birth. *Endocrinology* 2007, *148*, 878–885.

[48] Group HSCR, Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. *BJOG* 2010, *117*, 575–584.

[49] Catalano, P. M., Presley, L., Minium, J., Hauguel-de, M. S., Fetuses of obese mothers develop insulin resistance in utero. *Diabetes Care* 2009, *32*, 1076–1080.

[50] Mingrone, G., Manco, M., Mora, M. E., Guidone, C. et al., Influence of maternal obesity on insulin sensitivity and secretion in offspring. *Diabetes Care* 2008, *31*, 1872–1876.

[51] Nivoit, P., Morens, C., Van Assche, F. A., Jansen, E. et al., Established diet-induced obesity in female rats leads to offspring hyperphagia, adiposity and insulin resistance. *Diabetologia* 2009, *52*, 1133–1142.

[52] Shankar, K., Harrell, A., Liu, X., Gilchrist, J. M. et al., Maternal obesity at conception programs obesity in the offspring. *Am. J. Physiol.* 2008, *294*, R528–R538.

[53] Tamashiro, K. L., Terrillion, C. E., Hyun, J., Koenig, J. I. et al., Prenatal stress or high-fat diet increases susceptibility to diet-induced obesity in rat offspring. *Diabetes* 2009, *58*, 1116–1125.

[54] Cerf, M. E., Chapman, C. S., Louw, J., High-fat programming of hyperglycemia, hyperinsulinemia, insulin resistance, hyperleptinemia, and altered islet architecture in 3-month-old Wistar rats. *ISRN. Endocrinol.* 2012, *2012*, 627270.

[55] Cerf, M. E., Chapman, C. S., Muller, C. J., Louw, J., Gestational high-fat programming impairs insulin release and reduces Pdx-1 and glucokinase immunoreactivity in neonatal Wistar rats. *Metabolism* 2009, *58*, 1787–1792.

[56] Han, J., Xu, J., Epstein, P. N., Liu, Y. Q., Long-term effect of maternal obesity on pancreatic beta cells of offspring: reduced beta cell adaptation to high glucose and high-fat diet challenges in adult female mouse offspring. *Diabetologia* 2005, *48*, 1810–1818.

[57] Srinivasan, M., Katewa, S. D., Palaniyappan, A., Pandya, J. D. et al., Maternal high-fat diet consumption results in fetal malprogramming predisposing to the onset of metabolic syndrome-like phenotype in adulthood. *Am. J. Physiol.* 2006, *291*, E792–E799.

[58] Ford, S. P., Zhang, L., Zhu, M., Miller, M. M. et al., Maternal obesity accelerates fetal pancreatic beta-cell but not alpha-cell development in sheep: prenatal consequences. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2009, *297*, R835–R843.

[59] Zhang, L., Long, N. M., Hein, S. M., Ma, Y. et al., Maternal obesity in ewes results in reduced fetal pancreatic beta-cell numbers in late gestation and decreased circulating insulin concentration at term. *Domest. Anim. Endocrinol.* 2011, *40*, 30–39.

[60] Schaefer-Graf, U. M., Graf, K., Kulbacka, I., Kjos, S. L. et al., Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. *Diabetes Care* 2008, *31*, 1858–1863.

[61] Cottrell, E. C., Ozanne, S. E., Early life programming of obesity and metabolic disease. *Physiol. Behav*. 2008, *94*, 17–28.

[62] Wollmann, H. A., Intrauterine growth restriction: definition and etiology. *Horm. Res.* 1998, *49*, 1–6.

[63] Robinson, J. S., Moore, V. M., Owens, J. A., McMillen, I. C., Origins of fetal growth restriction. *Eur. J. Obst. Gynecol. Reprod. Biol.* 2000, *92*, 13–19.

[64] Simmons, R. A., Templeton, L. J., Gertz, S. J., Intrauterine growth retardation leads to the development of type 2 diabetes in the rat. *Diabetes* 2001, *50*, 2279–2286.

[65] Nusken, K. D., Dotsch, J., Rauh, M., Rascher, W. et al., Uteroplacental insufficiency after bilateral uterine artery ligation in the rat: impact on postnatal glucose and lipid metabolism and evidence for metabolic programming of the offspring by sham operation. *Endocrinology* 2008, *149*, 1056–1063.

[66] Gatford, K. L., Mohammad, S. N. B., Harland, M. L., De Blasio, M. J. et al., Impaired b-cell function and inadequate compensatory increases in b-cell mass following intrauterine growth restriction in sheep. *Endocrinology* 2008, *149*, 5118–5127.

[67] Haggarty, P., Allstaff, S., Hoad, G., Ashton, J. et al., Placental nutrient transfer capacity and fetal growth. *Placenta* 2002, *23*, 86–92.

[68] Bernstein, I. M., Horbar, J. D., Badger, G. J., Ohlsson, A., Golan, A., Morbidity and mortality among very-low-birthweight neonates with intrauterine growth restriction: the Vermont Oxford network. *Am. J. Obstet. Gynecol.* 2000, *182*, 198–206.

[69] Phipps, K., Barker, D. J., Hales, C. N., Fall, C. H. et al., Fetal growth and impaired glucose tolerance in men and women. *Diabetologia* 1993, *36*, 225–228.

[70] Ravelli, A. C. J., Van Der Meulen, J. H. P., Michels, R. P. J., Osmond, C. et al., Glucose tolerance in adults after prenatal exposure to famine. *Lancet* 1998, *351*, 173–177.

[71] Roseboom, T. J., Van Der Meulen, J. H., Osmond, C., Barker, D. J. et al., Adult survival after prenatal exposure to the Dutch famine 1944–45. *Paediatr. Perinat. Epidemiol.* 2001, *15*, 220–225.

[72] Ravelli, A. C., Der Meulen, J. H., Osmond, C., Barker, D. J. et al., Obesity at the age of 50 y in men and women exposed to famine prenatally. *Am. J. Clin. Nutr.* 1999, *70*, 811–816.

[73] Stanner, S. A., Yudkin, J. S., Fetal programming and the Leningrad Siege study. *Twin Res.* 2001, *4*, 287–292.

[74] Simmons, R., Developmental origins of adult metabolic disease: concepts and controversies. *Trends Endocrinol. Metab.* 2005, *16*, 390–394.

[75] Bhargava, S. K., Sachdev, H. S., Fall, C. H., Osmond, C. et al., Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. *N. Engl. J. Med.* 2004, *350*, 865–875.

[76] Whincup, P. H., Cook, D. G., Adshead, F., Taylor, S. J. C. et al., Childhood Size is more strongly related than size at birth to glucose and insulin levels in 10-11-year-old children. *Diabetologia* 1997, *40*, 319–326.

[77] Mericq, V., Ong, K. K., Bazaes, R., Pena, V. et al., Longitudinal changes in insulin sensitivity and secretion from birth to age three years in small- and appropriate-for-gestational-age children. *Diabetologia* 2005, *48*, 2609–2614.

[78] Eriksson, J., Forsén, T., Osmond, C., Barker, D., Obesity from cradle to grave. *Int. J. Obes.* 2003, *27*, 722–727.

[79] Vuguin, P. M., Animal models for small for gestational age and fetal programming of adult disease. *Horm. Res.* 2007, *68*, 113–123.

[80] Vuguin, P. M., Animal models for small for gestational age and fetal programming of adult disease. *Horm. Res* 2007, *68*, 113–123.

[81] Ross, M. G., Ervin, R. D., Leake, R. D., Fu, P. et al., Fetal lung liquid regulation by neuropeptides. *Am. J. Obstet. Gynecol.* 1984, *150*, 421–425.

[82] Wigglesworth, J. S., Fetal growth retardation. Animal model: uterine vessel ligation in the pregnant rat. *Am. J. Pathol.* 1974, *77*, 347–350.

[83] Garofano, A., Czernichow, P., Breant, B., In utero undernutrition impairs rat beta-cell development. *Diabetologia* 1997, *40*, 1231–1234.

[84] Hill, D. J., Duvillie, B., Pancreatic development and adult diabetes. *Pediatr. Res.* 2000, *48*, 269–274.

[85] Howie, G. J., Sloboda, D. M., Kamal, T., Vickers, M. H., Maternal nutritional history predicts obesity in adult offspring independent of postnatal diet. *J. Physiol.* 2009, *587*, 905–915.

[86] Ozaki, T., Nishina, H., Hanson, M. A., Poston, L., Dietary restriction in pregnant rats causes gender-related hypertension and vascular dysfunction in offspring. *J. Physiol.* 2001, *530*, 141–152.

[87] Dahri, S., Reusens, B., Remacle, C., Hoet, J. J., Nutritional influences on pancreatic development and potential links with non-insulin-dependent diabetes. *Proc. Nutr. Soc.* 1995, *54*, 345–356.

[88] Snoeck, A., Remacle, C., Reusens, B., Hoet, J. J., Effect of a low protein diet during pregnancy on the fetal rat endocrine pancreas. *Biol. Neonate* 1990, *57*, 107–118.

[89] Dahri, S., Snoeck, A., Reusens-Billen, B., Remacle, C. et al., Islet function in offspring of mothers on low-protein diet during gestation. *Diabetes* 1991, *40*, 115–120.

[90] Ozanne, S. E., Wang, C. L., Petry, C. J., Smith, J. M. et al., Ketosis resistance in the male offspring of protein-malnourished rat dams. *Metabolism* 1998, *12*, 1450–1454.

[91] Ozanne, S. E., Olsen, G. S., Hansen, L. L., Tingey, K. J. et al., Early growth restriction leads to down regulation of protein kinase C zeta and insulin resistance in skeletal muscle. *J. Endocrinol.* 2003, *177*, 235–241.

[92] Petry, C. J., Dorling, M. W., Pawlak, D. B., Ozanne, S. E. et al., Diabetes in old male offspring of rat dams fed a reduced protein diet. *Int. J. Exp. Diabetes Res.* 2001, *2*, 139–143.

[93] Gallo, L. A., Tran, M., Master, J. S., Mortiz, K. M. et al., Maternal adaptations and inheritance in the transgenerational programming of adult disease. *Cell Tissue Res.* 2012, *349*, 863–880.

[94] Boloker, J., Gertz, S. J., Simmons, R. A., Gestational diabetes leads to the development of diabetes in adulthood in the rat. *Diabetes* 2002, *51*, 1499–1506.

[95] Styrud, J., Eriksson, U. J., Grill, V., Swenne, I., Experimental intrauterine growth retardation in the rat causes a reduction of pancreatic b-cell mass, which persists into adulthood. *Biol. Neonate* 2005, *88*, 122–128.

[96] De Prins, F. A., Van Assche, F. A., Intrauterine growth retardation and development of endocrine pancreas in the experimental rat. *Biol. Neonate* 1982, *41*, 16–21.

[97] Vuguin, P., Raab, E., Liu, B., Barzilai, N. et al., Hepatic insulin resistance precedes the development of diabetes in a model of intrauterine growth-retardation. *Diabetes* 2004, *53*, 2617–2622.

[98] Simmons, R. A., Role of metabolic programming in the pathogenesis of beta-cell failure in postnatal life. *Rev. Endocr. Metab. Dis.* 2007, *8*, 95–104.

[99] Selak, M. A., Storey, B. T., Peterside, I., Simmons, R. A., Impaired oxidative phosphorylation in skeletal muscle of intrauterine growth-retarded rats. *Am. J. Physiol.* 2003, *285*, E130–E137.

[100] Lane, R. H., Maclennan, N. K., Hsu, J. L., Janke, S. M. et al., Increased hepatic peroxisome proliferator-activated receptor-gamma coactivator-1 gene expression in a rat model of intrauterine growth retardation and subsequent insulin resistance. *Endocrinology* 2002, *143*, 2486–2490.

[101] Wadley, G. D., Siebel, A. L., Cooney, G. J., McConell, G. K. et al., Uteroplacental insufficiency and reducing litter size alters skeletal muscle mitochondrial biogenesis in a sex specific manner in the adult rat. *Am. J. Physiol.* 2008, *294*, 861–869.

[102] Siebel, A. L., Mibus, A., De Blasio, M. J., Westcott, K. T. et al., Improved lactational nutrition and postnatal growth ameliorates impairment of glucose tolerance by uteroplacental insufficiency in male rat offspring. *Endocrinology* 2008, *149*, 3067–3076.

[103] Laker, R. C., Gallo, L. A., Wlodek, M. E., Siebel, A. L. et al., Short-term exercise training early in life restores deficits in pancreatic b-cell mass associated with growth restriction in adult male rats. *Am. J. Physiol.* 2011, *301*, 931–940.

[104] Siebel, A. L., Gallo, L. A., Guan, T. C., Owens, J. A. et al., Cross-fostering and improved lactation ameliorates deficits in endocrine pancreatic morphology in growth restricted adult male rat offspring. *J. Dev. Orig. Health Dis.* 2010, *1*, 234–244.

[105] Gallo, L. A., Tran, M., Moritz, K. M., Mazzuca, M. Q. et al., Cardio-renal and metabolic adaptations during pregnancy in female rats born small: implications for maternal health and second generation fetal growth. *J. Physiol.* 2012, *590*, 617–630.

[106] Gluckman, P. D., Hanson, M. A., Pinal, C., The developmental origins of adult disease. *Matern. Child Nutr.* 2005, *1*, 130–141.

[107] Harding, J. E., The nutritional basis of the fetal origins of adult disease. *Int. J. Epidemiol.* 2001, *30*, 15–23.

[108] Monteiro, P. O., Victora, C. G., Rapid growth in infancy and childhood and obesity in later life—a systematic review. *Obes. Rev.* 2005, *6*, 143–154.

[109] Baird, J., Fisher, D., Lucas, P., Kleijnen, J. et al., Being big or growing fast: systematic review of size and growth in infancy and later obesity. *BMJ* 2005, *331*, 929.

[110] Euser, A. M., Finken, M. J. J., Keijzer-Veen, M. G., Wit, J. M. et al., Associations between prenatal and infancy weight gain and BMI, fat mass, and fat distribution in young adulthood: a prospective cohort study in males and females born very preterm. *Am J Clin Nutr* 2005, *81*, 480–487.

[111] Finken, M. J., Keijzer-Veen, M. G., Dekker, F. W., Frolich, M. et al., Preterm birth and later insulin resistance: effects of birth weight and postnatal growth in a population based longitudinal study from birth into adult life. *Diabetologia* 2006, *49*, 478–485.

[112] Ong, K. K., Ahmed, M. L., Emmett, P. M., Preece, M. A. et al., Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *Br. Med. J.* 2000, *320*, 967–971.

[113] Malina, R. M., Katzmarzyk, P. T., Beunen, G., Birth weight and its relationship to size attained and relative fat distribution at 7 and 12 years of age. *Obes. Res.* 1996, *4*, 385–390.

[114] Zetterström, K., Lindeberg, S., Haglund, B., Magnuson, A. et al., Being born small for gestational age incraeses the risk of severe pre-eclampsia. *J. Obstet. Gynaecol.* 2007, *114*, 319–324.

[115] Klebanoff, M. A., Secher, N. J., Mednick, B. R., Schulsinger, C., Maternal size at birth and the development of hypertension during pregnancy: a test of the Barker hypothesis. *Arch. Intern. Med.* 1999, *159*, 1607–1612.

[116] Seghieri, G., Anichini, R., De Bellis, A., Alviggi, L. et al., Relationship between gestational diabetes mellitus and low maternal birth weight. *Diabetes Care* 2002, *25*, 1761–1765.

[117] Artal, R., Catanzaro, R. B., Gavard, J. A., Mostello, D. J. et al., A lifestyle intervention of weight-gain restriction: diet and exercise in obese women with gestational diabetes mellitus. *Appl. Physiol. Nutr. Metab.* 2007, *32*, 596–601.

[118] Ong, M. J., Guelfi, K. J., Hunter, T., Wallman, K. E. et al., Supervised home-based exercise may attenuate the decline of glucose tolerance in obese pregnant women. *Diabetes Metab.* 2009, *35*, 418–421.

[119] Liu, J. H., Mayer-Davis, E. J., Pate, R. R., Gallagher, A. E. et al., Physical activity during pregnancy is associated with reduced fasting insulin—the Pilot Pregnancy and Active Living Study. *J. Matern. Fetal Neonatal Med.* 2010, *23*, 1249–1252.

[120] van Poppel, M. N., Oostdam, N., Eekhoff, M. E., Wouters, M. G. et al., Longitudinal relationship of physical activity with insulin sensitivity in overweight and obese pregnant women. *J. Clin. Endocrinol. Metab.* 2013, *98*, 2929–2935.

[121] Callaway, L. K., Colditz, P. B., Byrne, N. M., Lingwood, B. E. et al., Prevention of gestational diabetes: feasibility issues for an exercise intervention in obese pregnant women. *Diabetes Care* 2010, *33*, 1457–1459.

[122] Dodd, J. M., Turnbull, D., Mcphee, A. J., Deussen, A. R. et al., Antenatal lifestyle advice for women who are overweight or obese: LIMIT randomised trial. *BMJ* 2014, *348*, g1285.

[123] Zhang, C., Solomon, C. G., Manson, J. E., Hu, F. B., A prospective study of pregravid physical activity and sedentary behaviors in relation to the risk for gestational diabetes mellitus. *Arch. Intern. Med.* 2006, *166*, 543–548.

[124] Oken, E., Ning, Y., Rifas-Shiman, S. L., Radesky, J. S. et al., Associations of physical activity and inactivity before and during pregnancy with glucose tolerance. *Obstet. Gynecol.* 2006, *108*, 1200–1207.

[125] Dempsey, J. C., Butler, C. L., Sorensen, T. K., Lee, I. M. et al., A case-control study of maternal recreational physical activity and risk of gestational diabetes mellitus. *Diabetes Res. Clin. Pract.* 2004, *66*, 203–215.

[126] Vega, C. C., Reyes-Castro, L. A., Bautista, C. J., Larrea, F. et al., Exercise in obese female rats has beneficial effects on maternal and male and female offspring metabolism. *Int. J. Obes.* 2015, *39*, 712–719.

[127] Raipuria, M., Bahari, H., Morris, M. J., Effects of maternal diet and exercise during pregnancy on glucose metabolism in skeletal muscle and fat of weanling rats. *PLoS One* 2015, *10*, e0120980.

[128] Stanford, K. I., Lee, M. Y., Getchell, K. M., So, K. et al., Exercise before and during pregnancy prevents the deleterious effects of maternal high-fat feeding on metabolic health of male offspring. *Diabetes* 2015, *64*, 427–433.

