Maternal Lifestyle Factors and Fetal Macrosomia Risk: A Review

Redfern, KM; Rees, GA; Pinkney, JH

Published in:
EMJ Reproductive Health

Publication date:
2016

Maternal Lifestyle Factors and Fetal Macrosomia Risk: A Review

Kathy M. Redfern, Dr Gail A. Rees and Professor Jonathan H. Pinkney

Peninsula Schools of Medicine and Dentistry, Plymouth University, Plymouth, United Kingdom.

Corresponding Author:
Miss Kathy Redfern
C507 Portland Square
School of Biomedical and Healthcare Sciences
Plymouth University
Drake Circus
Plymouth
PL4 8AA

Email: kathy.redfern@plymouth.ac.uk

Word count: 2996

Maternal Lifestyle Factors and Fetal Macrosomia Risk: A Review.

Kathy M. Redfern, Gail A. Rees and Jonathan H. Pinkney.

Abstract:

Fetal macrosomia is associated with a number of health complications for both mother and infant in the immediate, short and long term. Maternal obesity and excessive gestational weight gain have long been associated with fetal macrosomia, however, the impact of maternal lifestyle factors such as dietary intake and energy balance, in combination with the timing and composition of weight gain have been less studied. It is also clear that although maternal obesity and excessive gestational weight gain increase the risk of fetal macrosomia independently, the risk is magnified with the presence of both risk factors, suggesting that interventions to control gestational weight gain may be particularly important for obese women. Association studies examining the relationship between fetal nutrient availability, epigenetic modifications and infant anthropometrics are also required. This review provides an overview of the current evidence examining the role of maternal lifestyle factors on the prevalence of fetal macrosomia and identifies areas where further research is required in order to inform the design of appropriate intervention strategies.

Keywords: Birth weight, body composition, gestational weight gain, macrosomia, maternal obesity.

Birth weight is a key determinant of infant health which appears to be determined by a complex interaction of maternal and fetal factors. These probably include maternal genetic, environmental and lifestyle factors, in conjunction with fetal genetic and intrauterine environmental factors. Macrosomia is generally defined as a birth weight greater than 4000g or 4500g, irrespective of gestational age[1], while large for gestational age (LGA) is defined as a birth weight >90th percentile as per gestational age[2].

Excessive fetal growth results in increased immediate, short term and long term risks for both mother and infant. Macrosomia increases the risk of complications during delivery such as birth asphyxia and shoulder dystocia, and also carries an increased risk of delivery via caesarean section, which carries its own adverse risks to both neonate and mother[3]. Furthermore, higher birth weight is also associated with increased risk of obesity[4] and metabolic syndrome[5] into childhood, which pose serious long term health risks.

Numerous maternal factors such as body mass index (BMI), gestational weight gain (GWG), diet, physical activity and the development of gestational diabetes have been shown to impact infant birth weight, however previous studies have tended to examine these factors individually, and their interaction less so. The purpose of this review is to critically appraise the current literature and highlight areas where further research is required to inform appropriate maternal intervention strategies, with the aim of improving the health of newborn offspring.

Maternal Weight

When examined individually, maternal pre-pregnancy BMI tends to be strongly associated with an increased risk of macrosomia. Numerous studies have observed women classified by their BMI as obese to be at significantly greater risk of macrosomia compared with women classified as having a healthy weight,[6,7] with risk increasing as BMI increases beyond the healthy range[8] A recent systematic review and meta-analysis conducted by Gaudet and colleagues[1] showed a positive relationship between maternal obesity and fetal overgrowth as defined by birth weight ≥ 4000g, ≥ 4500g and ≥ 90th percentile for gestational age.

Similarly, excessive GWG has been shown to increase risk of macrosomia[9-11] and so, although it seems clear that both maternal obesity and excess GWG independently increase the risk of macrosomia, the interaction between the two factors is less clear. Crane et al.[12] conducted a retrospective cohort study evaluating the effects of GWG on maternal and neonatal outcomes in different BMI classes. In keeping with findings from previous studies[6-8] they observed that overweight and obese mothers were significantly more likely to give birth to a macrosomic infant (birth weight ≥ 4000g and adjusted for gestational age) and also more likely to gain excess weight than healthy weight mothers. However, when the impact of GWG on risk of macrosomic infant was examined by BMI class, risk increased with excess GWG for all BMI classes suggesting that when excessive GWG does occur, the risk of macrosomia increases regardless of pre-pregnancy BMI. A major limitation of this study was that it was retrospective, and so pre-pregnancy BMI or GWG data were missing for 47.8% of women. Nohr et al.[13] conducted a similar study reporting that BMI category was a stronger predictor of LGA neonate than GWG, but that very high GWG (defined as >20kg) increased the absolute risk of LGA neonate across all BMI categories. Limitations of the study were

that pre-pregnancy weight, height and GWG were self-reported , the reliability of which has been disputed[14]. In addition to examining the effect of maternal obesity and GWG on infant birth weight, Carlsen and colleagues[15] included neonatal body composition as an outcome measure. They observed that infants born to obese mothers were heavier than infants born to healthy weight mothers, and this was exclusively due to increased adiposity. GWG on the other hand, was found to increase both fat mass, abdominal fat mass and fat free mass. Obese mothers were more likely to exhibit excessive GWG, thereby suggesting these women as a particularly important target group to receive an intervention with an aim of reducing fetal macrosomia.

The effect of GWG on maternal and neonatal outcomes in women classified as having a healthy pre-pregnancy BMI was examined by Deruelle and colleagues[16]. Although most neonatal outcomes were similar between GWG groups, mean birth weight was significantly greater in women with ≥18kg GWG than women gaining 9-15kg, while the proportion of macrosomic neonates more than doubled for women with ≥18kg GWG compared those gaining 9-15kg (12.1% vs. 5.2%, $P<0.03$). Prevention of excess GWG in women of healthy pre-pregnancy BMI is therefore also important, just as in overweight or obese mothers. In 2009, the Institute of Medicine (IOM) published a new set of guidelines on GWG to replace those previously published in 1990[11] and now make recommendations based on pre-pregnancy BMI category for total and rate of weight gain.

is suggested that birth weight, and early childhood growth patterns can lead to a predisposition to childhood obesity, with the potential to persist into adolescence and adulthood[17]. In a diverse sample of US women, adequate GWG, when compared with inadequate weight gain, was associated with significantly increased odds of infants being

born small for gestational age (SGA), while excessive gain was significantly associated with decreased odds of SGA and more than doubled the risk of LGA[18]. Excessive GWG also significantly increased the risk of child overweight or obesity (BMI ≥ 85th percentile) when followed up between the ages of 2 and 20 years. For overweight and obese women, predicted probabilities of LGA and childhood overweight were higher than those for underweight or healthy weight women, regardless of GWG. Increased GWG was significantly associated with increased probability of LGA and child overweight across all BMI groups. Similarly, a retrospective cohort of 499 mother-child dyads[19] observed that maternal morbid obesity (BMI ≥40 kg/m^2) was significantly associated with infant birth weight and weight for length throughout the first 3 months of life, and that these associations were significantly amplified by excess GWG. At 12 months of age these effects were sustained, with infants of morbidly obese mothers exhibiting an 8.4% higher weight for length percentile compared with infants of mothers with a BMI of 25 kg/m^2. Infants born to mothers with a healthy BMI, but with excess GWG normalised their growth by 12 months of age.

These findings suggest that babies born to women in all BMI categories are at risk of increased birth weight and elevated weight during early life as a result of excessive GWG, but that overweight and obese women are of particular concern, as their risk appears to be amplified[15,19]. Future studies, particularly of a prospective nature should therefore perhaps focus on this group of women in order to develop a wider understanding of lifestyle factors that contribute to excess GWG.

Maternal Body Composition:

Although BMI is widely used to provide estimates of body composition, it is not without its limitations. Prentice & Jebb[20] propose that obesity should be defined as the excess accumulation of body fat, whereas BMI identifies the presence of excess body weight, which also reflects lean body mass. Krentz et al.[21] compared birth weight outcomes for women with the same BMI, but two different heights in a retrospective cohort study. They observed differences in birth weights and birth weight classification by gestational age between groups, which once again provides evidence to suggest the limited utility of BMI as a predictor of neonatal outcomes. In addition, GWG is typically reported as a single measure of mass gained during pregnancy, with the individual effects of fat mass and fat-free mass gains left undefined. It therefore seems prudent to examine the contributions of changes to estimated maternal fat mass and fat free mass on pregnancy outcomes, in addition to total GWG and maternal obesity defined by BMI.

As might be expected, maternal weight, fat-free mass and fat mass increased between 28 and 37 weeks gestation in a recent prospective cohort study examining maternal body composition, however, birth weight significantly correlated with maternal fat-free mass and not fat mass[22]. In a similar study fat-free mass, but not fat mass was also a significant predictor of birth weight, and after adjustment for confounding variables, mothers in the highest fat-free mass quartile were at significantly higher risk of infant macrosomia, compared with mothers in the lowest quartile[23]. However, this study measured body composition only in the first trimester. Butte et al.[24] partitioned GWG into fat mass, fat-free mass, total body water and protein gains as assessed at weeks 9, 22 and 36 of gestation. Infant birth weight was found to correlate significantly with fat-free mass ($r= 0.39$, $P=0.003$) and total body water ($r= 0.37$, $P=0.006$), but not fat mass ($r= 0.05$, $P = 0.76$). These studies

suggest fat-free mass, and not fat mass mediates an increase in infant birth weight. It is hypothesised that these positive associations between maternal fat free mass and infant birth weight may be due to maternal plasma volume expansion[25], which is in turn influenced by maternal hormonal changes[26].

Forsum et al.[27] addressed the hypothesis that maternal body fat stimulates fetal growth and fat deposition. In a small, observational study they assessed infant subcutaneous adipose tissue volume in vivo using magnetic resonance imaging, while maternal body composition was assessed using a two-compartment model based on total body water. It was observed that maternal total body fat before pregnancy and at 32 weeks gestation were significantly and positively correlated with infant birth weight, while in infants, birth weight positively correlated with subcutaneous adipose tissue.

Further studies examining the effects of maternal body composition on neonatal body composition and incidence of macrosomia are therefore required in order to fully understand the relationship between the composition of GWG and infant birth size.

Timing of Gestational Weight Gain:

Although the influence of total GWG during pregnancy has been well documented, the timing of overnutrition and subsequent weight gain has not been examined as thoroughly. This could be an important factor in the design of any intervention studies. Davenport et al.[28] evaluated whether the timing of excessive GWG in pregnant women following current healthy living guidelines affected neonatal adiposity at birth in their prospective cohort study. The cohort were retrospectively grouped according to IOM guidelines[11] for weight gain in the first and second halves of pregnancy. Infants born to women who exhibited

excessive GWG during the first half of pregnancy exhibited greater birth weight, crown-heel length and excessive neonatal body fat compared with infants born to women who exhibited appropriate GWG in the first half of pregnancy. These differences remained significant after controlling for BMI, total GWG, maternal age, gestational age and neonatal sex. Farah et al.[22] conducted a longitudinal prospective observational study which observed that birth weight was significantly correlated with GWG before the third trimester (r=0.163, P=0.027) but not with total or third trimester GWG. These studies suggest that neonatal adiposity is potentially more strongly influenced by timing of GWG than total GWG, suggesting a direct link between the early intrauterine environment and subsequent neonatal adiposity. However, the data on timing of GWG and its influence on neonatal weight and adiposity is limited. Studies examining weight change during pregnancy at frequent assessments are therefore required in order to increase our understanding of the mechanism by which maternal obesity and GWG influence infant birth weight and body composition.

Gestational Diabetes Mellitus:

Gestational diabetes mellitus (GDM) is a common metabolic complication of pregnancy, defined as glucose intolerance with first onset or recognition during pregnancy[29]. GDM is most frequently observed amongst overweight or obese women[30] as these women are more likely to exhibit impaired glucose tolerance and decreased insulin sensitivity before and during pregnancy[31] when compared with women of a healthy weight. Infants born to women with GDM are often characterised by excessive fetal growth and subsequently tend to be at increased risk of macrosomia[31]. However, even in the absence of increased body mass, studies have shown that infants born to mothers with GDM exhibit increases in fat

mass, but not fat-free mass when compared with women with normal glucose tolerance[32,33]. Results from the hyperglycaemia and adverse pregnancy outcome (HAPO) study observed an increase in neonatal adiposity associated with increasing maternal glucose concentrations, less than those used to define GDM[34]. Physical activity has also been shown to influence glucose metabolism and transport via insulin-independent pathways, and has been associated with a decreased incidence of GDM in epidemiological studies[35].

Maternal Energy Intake and Expenditure:

Clearly nutritional status prior to and during pregnancy is essential for the growth and development of the foetus, with excessive GWG and adverse pregnancy outcomes also largely influenced by dietary intake, either as nutrient excess, nutrient deficiencies or by indirectly influencing the intrauterine environment.

A study by Knudson et al.[36] supports the theory that maternal glucose metabolism may impact fetal growth. They examined the associations between maternal glycaemic load, GWG, birth weight and risk of LGA neonate as part of the Danish National Birth Cohort. They observed that the risk of LGA neonate increased by 14% for the highest glycaemic load quintile, compared with the lowest quintile. A randomised controlled trial examining the impact of a low glycaemic index diet on neonatal anthropometry observed a decrease in neonatal thigh circumference for the intervention group when compared with a control group, although no differences were observed for any skinfold measurements nor head, abdominal or mid-upper arm circumferences[37].

In a prospective study, GWG was significantly and positively associated with energy intake and energy-adjusted intakes of lipids from animal origin and protein, while a significant

inverse association was observed between carbohydrate intake and GWG, but these were not significantly related to birth size[38]. Olsen et al.[39] observed that milk consumption during pregnancy was inversely associated with SGA, and directly associated with LGA and mean birth weight. Women consuming ≥ 6 glasses of milk/day had increased risk of LGA infants when compared with women who reported no milk consumption. When fat and protein intakes from dairy products (excluding cheese and ice cream) were examined, no association between birth weight and fat intake was found, while a positive association between protein intake and birth weight was observed. The authors proposed that the positive association between milk consumption and birth weight is driven by the presence of insulin-like growth factor-1 in both low-fat and whole-milk products. Montpetit et al.[40] examined the contribution of pre-pregnancy BMI, energy intake and physical activity as determinants of GWG and infant birth weight. Energy intake was the only significant predictor of infant birth weight. Steps per day were inversely associated with GWG, although when pre-pregnancy BMI was added to the model, steps were no longer significant and BMI remained the only significant variable.

A U.S. study[41] observed decreases in birth weight and LGA births between 2000 and 2005, trends which did not appear to be explained by routinely recorded maternal characteristics. The authors hypothesised that other maternal characteristics such as maternal diet, physical activity or socioeconomic factors may have contributed to the trends observed and called for detailed studies of smaller populations to explore the role of these factors.

Furthermore, the rapidly expanding field of epigenetic epidemiology has observed numerous associations between fetal nutrient availability and epigenetic modifications[42].

Differences in the methylation status of candidate genes have been observed in relation to fetal growth[43] and later childhood adiposity,[44,45] however, human studies examining specific intrauterine nutritional exposures and subsequent adiposity at birth and during childhood are scarce. Studies of an observational and epigenetic nature are therefore essential for increasing our understanding of how nutritional exposures influence GWG and infant phenotypic outcomes.

Conclusion:

It is important to gain an understanding of the factors influencing neonatal anthropometric outcomes, as macrosomic infants with or without excess adiposity at birth have been shown to be at increased risk of adverse consequences such as insulin resistance,[46,47] metabolic syndrome[5] and childhood obesity[4,48]. As observed from the current literature, there is consistent evidence to suggest that maternal obesity and excess GWG alongside GDM contribute to increased risk of adverse neonatal anthropometric outcomes,[12,13] hence current pregnancy interventions already aim to reduce the prevalence of these risk factors. . However, maternal obesity and GWG are broad outcome measures. Recent studies suggest maternal body composition, and timing of GWG may influence infant anthropometrics independently of maternal BMI and total GWG which may offer an increased understanding of the mechanisms by which maternal obesity and GWG influence neonatal anthropometric outcomes. At present, data in this area is limited[22,23,28] and there is also a lack of recent prospective studies examining the effects of GWG by BMI according to the most recent IOM recommendations[11].

Maternal diet and energy balance during pregnancy undoubtedly influence GWG and subsequent anthropometric outcomes for offspring. However, despite a wealth of studies

linking maternal energy intake to GWG,[38,49] and maternal dietary glucose intake to neonatal anthropometry,[36,37] few studies have examined the impact of other nutrients in the maternal diet, nor energy balance together with physical activity. Studies examining nutritional exposures during pregnancy and epigenetic modifications in offspring are also required[50].

The contributions of various maternal lifestyle factors to fetal macrosomia from the current literature are summarised in Table 1. However, as discussed, there are gaps in the current literature, as well as conflicting findings. It is therefore necessary to examine further the independent and moderating effects of maternal dietary intake, physical activity and the timing and composition of GWG, on neonatal anthropometric outcomes in future studies. Such studies could provide a more complete picture of the maternal lifestyle factors contributing to GWG, neonatal body composition and potentially, future offspring health, thus allowing health professionals to develop suitable and effective interventions to improve birth and health outcomes for both mother and infant. In the meantime, pregnant women should be advised to adhere to IOM guidelines for weight gain[11] and offered nutritional support if necessary. Particularly close attention should be paid to women entering their pregnancy with a BMI ≥30, as offspring of these women appear to be at increased risk of macrosomia, regardless of the contribution of other potential risk factors yet to be investigated.

Conflict of Interest Statement:

We have no conflict of interest to declare.

Table 1. The contributions of maternal lifestyle factors to risk of macrosomia.

	Risk of macrosomia/ LGA/higher birth weight increased…	Risk of macrosomia/LGA/higher birth weight unaffected …
Maternal pre-pregnancy BMI ≥25 kg/m^2	✓ [1, 6-8, 18]	
Gestational Diabetes Mellitus	✓ [31-34]	
Excess total GWG	✓ [9,10,16,18]	✓ [22]
Maternal obesity and excess total GWG.	✓ [12,13,15,19]	
Early excessive GWG (1st or 2nd trimester)	✓ [22,28]	
GWG in 3rd trimester		✓ [22]
Maternal fat mass	✓ [27]	✓ [22,24]
Maternal fat free mass	✓ [22-24]	
Dietary energy intake	✓ [40]	✓ [38]
Dietary fat intake		✓ [39,51]
Dietary protein intake	✓ [39]	
Milk consumption	✓ [39]	
Glycaemic Load	✓ [36, 37]	
Physical activity		✓ [8, 40]

REFERENCES

1. Gaudet L et al. Maternal obesity and occurrence of fetal macrosomia: a systematic review and meta-analysis. Biomed Res Int. 2014;2014:640291.

2. Surkan, PJ et al., Reasons for Increasing Trends in Large for Gestational Age Births. Obstet Gynecology. 2004; 104(4): 720-726.

3. Bérard J et al. Fetal macrosomia: risk factors and outcome: A study of the outcome concerning 100 cases >4500 g. Eur J Obstet Gynecol Reprod Biol. 1998;77(1):51-9.

4. Whitaker RC. Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy. Pediatrics. 2004;114(1):e29-36.

5. Boney CM et al. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics. 2005;115(3):e290-6.

6. Scott-Pillai R et al. The impact of body mass index on maternal and neonatal outcomes: a retrospective study in a UK obstetric population, 2004-2011. BJOG. 2013;120(8):932-9.

7. Bhattacharya S et al. Effect of Body Mass Index on pregnancy outcomes in nulliparous women delivering singleton babies. BMC Public Health. 2007;7(1):168.

8. Dodd JM et al. Maternal and perinatal health outcomes by body mass index category. Aust N Z J Obstet Gynaecol. 2011;51(2):136-40.

9. Savitz DA et al. Gestational weight gain and birth outcome in relation to prepregnancy body mass index and ethnicity. Ann Epidemiol. 2011;21(2):78-85.

10. Rodrigues PL et al. Determinant factors of insufficient and excessive gestational weight gain and maternal-child adverse outcomes. Nutrition. 2010;26(6):617-23.

11. Rasmussen K, Yaktine A (eds.) Weight Gain During Pregnancy: Reexamining the guidelines (2009), Washington, D.C.: The National Academies Press.

12. Crane JM et al. The effect of gestational weight gain by body mass index on maternal and neonatal outcomes. J Obstet Gynaecol Can. 2009;31(1):28-35.

13. Nohr EA et al. Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy. Am J Clin Nutr. 2008;87(6):1750-9.

14. Stewart AL. The reliability and validity of self-reported weight and height. J Chronic Dis, 1982;35(4):295-309.

15. Carlsen EM et al. Newborn regional body composition is influenced by maternal obesity, gestational weight gain and the birthweight standard score. Acta Paediatr. 2014;103(9):939-45.

16. Deruelle P et al. Maternal and fetal consequences of increased gestational weight gain in women of normal prepregnant weight. Gynecol Obstet Fertil. 2004;32(5):398-403.

17. Taveras EM et al. Weight status in the first 6 months of life and obesity at 3 years of age. Pediatrics. 2009;123(4):1177-83.

18. Margerison Zilko CE et al. Association of maternal gestational weight gain with short- and long-term maternal and child health outcomes. Am J Obstet Gynecol. 2010;202(6):574.e1-8.

19. Heerman WJ et al. Interaction between Maternal Prepregnancy Body Mass Index and Gestational Weight Gain Shapes Infant Growth. Acad Pediatr. 2014;14(5):463-70.

20. Prentice AM, Jebb SA. Beyond body mass index. Obes Rev. 2001;2(3):141-7.

21. Krentz, H et al. On the Variability in Preterm Birth Rate, Birth Weight, and Somatic Classification among Neonates of Mothers with the Same Body Mass Index. Z Geburtshilfe Neonatol. 2011; 215(04): 163-166.

22. Farah N et al. The influence of maternal body composition on birth weight. Eur J Obstet Gynecol Reprod Biol. 2011;157(1):14-7.

23. Kent E et al. Correlation between birth weight and maternal body composition. Obstet Gynecol. 2013;121(1):46-50.

24. Butte NF et al. Composition of gestational weight gain impacts maternal fat retention and infant birth weight. Am J Obstet Gynecol. 2003;189(5):1423-32.

25. Rosso P (ed). Nutrition and Metabolism in Pregnancy: mother and fetus (1990), Oxford: Oxford University Press.

26. Salas SP et al. Maternal plasma volume expansion and hormonal changes in women with idiopathic fetal growth retardation. Obstet Gynecol. 1993;81(6):1029-33.

27. Forsum E et al. Maternal body composition in relation to infant birth weight and subcutaneous adipose tissue. Br J Nutr. 2006;96(2):408-14.

28. Davenport MH et al. Timing of excessive pregnancy-related weight gain and offspring adiposity at birth. Obstet Gynecol. 2013;122(2 Pt 1):255-61.

29. American Diabetes Association, Gestational Diabetes Mellitus. Diabetes Care. 2003;26:s103-s105.

30. Chu SY et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes care. 2007;30(8):2070-6.

31. Catalano PM. The impact of gestational diabetes and maternal obesity on the mother and her offspring. J Dev Orig Health Dis. 2010;1(4):208-15.

32. Catalano PM et al. Increased fetal adiposity: a very sensitive marker of abnormal in utero development. Am J Obstet Gynecol. 2003;189(6):1698-704.

33. Durnwald C et al. Evaluation of body composition of large-for-gestational-age infants of women with gestational diabetes mellitus compared with women with normal glucose tolerance levels. Am J Obstet Gynecol. 2004;191(3):804-8.

34. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. Diabetes. 2009;58(2):453-9.

35. Zhang C, Ning Y. Effect of dietary and lifestyle factors on the risk of gestational diabetes: review of epidemiologic evidence. Am J Clin Nutr. 2011;94(6 Suppl):1975S-1979S.

36. Knudsen VK et al. Maternal dietary glycaemic load during pregnancy and gestational weight gain, birth weight and postpartum weight retention: a study within the Danish National Birth Cohort. Br J Nutr. 2013;109(8):1471-8.

37. Donnelly JM et al. Impact of maternal diet on neonatal anthropometry: a randomized controlled trial. Pediatr Obes. 2015;10(1):52-6.

38. Lagiou P et al. Diet during pregnancy in relation to maternal weight gain and birth size. Eur J Clin Nutr. 2004;58(2):231-7.

39. Olsen SF et al. Milk consumption during pregnancy is associated with increased infant size at birth: prospective cohort study. Am J Clin Nutr. 2007;86(4):1104-10.

40. Montpetit AE et al. Modeling the impact of prepregnancy BMI, physical activity, and energy intake on gestational weight gain, infant birth weight, and postpartum weight retention. J Phys Act Health. 2012;9(7):1020-9.

41. Donahue, SMA et al. Trends in Birth Weight and Gestational Length Among Singleton Term Births in the United States: 1990–2005. Obstet Gynecol. 2010; 115(2 Pt 1): 357-364.

42. Rakyan VK et al. Epigenome-wide association studies for common human diseases. Nat Rev Genet. 2011;12(8):529-41.

43. Drake AJ et al. An unbalanced maternal diet in pregnancy associates with offspring epigenetic changes in genes controlling glucocorticoid action and foetal growth. Clin Endocrinol (Oxf). 2012;77(6):808-15.

44. Godfrey KM et al. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. Diabetes. 2011;60(5):1528-34.

45. Clarke-Harris R et al. PGC1α Promoter Methylation in Blood at 5–7 Years Predicts Adiposity From 9 to 14 Years (EarlyBird 50). Diabetes. 2014;63(7):2528-37.

46. Catalano PM et al. Fetuses of obese mothers develop insulin resistance in utero. Diabetes Care. 2009;32(6):1076-80.

47. The HAPO Study Cooporerative Research Group. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. BJOG. 2010;117(5):575-84.

48. Mamun AA et al. Gestational weight gain in relation to offspring obesity over the life course: a systematic review and bias-adjusted meta-analysis. Obes Rev. 2014;15(4):338-47.

49. Stuebe AM et al. Associations of diet and physical activity during pregnancy with risk for excessive gestational weight gain. Am J Obstet Gynecol. 2009;201(1):58.e1-8.

50. Rando OJ, Simmons RA. I'm eating for two: parental dietary effects on offspring metabolism. Cell. 2015;161(1):93-105.

51. Guelinckx I et al. Effect of lifestyle intervention on dietary habits, physical activity, and gestational weight gain in obese pregnant women: a randomized controlled trial. Am J Clin Nutr. 2010;91(2):373-80.