

Large for Gestational Age and Obesity-Related Comorbidities

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Both small for gestational age and large for gestational age (LGA) size at birth are associated with metabolic complications throughout life. The long-term consequences of LGA have been investigated in only a few studies. LGA is thought to be associated with early obesity and metabolic risk. Understanding how LGA can influence later obesity risk is important for pediatric obesity interventions. Pregnant women who are overweight or obese are at high risk of having LGA babies. Infants born LGA are at increased risk of becoming overweight or obese children, adolescents, and young adults and can have an increased risk of metabolic syndrome later in life and giving birth to LGA offspring. Education and intervention for weight control before and during pregnancy should be conducted to prevent LGA births. Particular attention is needed for women of childbearing age who are diabetic and obese, which could be the starting point for lifelong management of obesity.

Key words: Gestational age, Birth weight, Obesity, Comorbidity

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INTRODUCTION

Large for gestational age (LGA) describes a neonate who, at birth, weighs at or above the 90th percentile for gestational age.¹ Though the terms LGA and macrosomia have been used interchangeably, but LGA is more precise.² Macrosomia tends to refer to babies with birth weight > 4,000 g.³ Both low and high birth weight are associated with metabolic complications later in life.^{4,5} The association between gestational age and later chronic diseases was proposed first by Barker et al.,⁶ and results of many epidemiologic studies have supported this hypothesis. Many investigators have studied small for gestational age (SGA) and obesity-related morbidities; however, LGA studies are sparse. To date, the long-term consequences of LGA have not been defined.

The incidence of infants born LGA has been reported to vary

globally by region. During recent decades, LGA births have increased 15%–20% in several developed countries.⁷ In the 1920s, LGA was associated with reduced morbidity and mortality in the seventh decade of life compared with babies born with lower birth weight.^{6,8} However, in the past 30 years, with changes in postnatal environmental conditions and increasing obesity, LGA appears to increase early obesity and cardiovascular and metabolic risk.^{9,10}

Understanding how high birth weight can produce risk of obesity in later life is important for pediatric obesity interventions. An increasing relationship between birth weight and childhood obesity has been observed.⁹ In epidemiological studies, high birth weight was associated with higher risk of hypertension, type 2 diabetes mellitus (T2DM), cardiovascular disease, and certain forms of cancer later in life.^{10,11} This review discusses recent studies focused on the risk of childhood obesity and obesity-related morbidities in in-

fants born LGA. The results will provide insight into childhood growth monitoring and aid future research regarding prevention of LGA-related morbidity.

LGA AND RISK FACTORS

Fetal overgrowth is caused by genetic and maternal factors. Genetic factors include several syndromes including Beckwith-Wiedemann syndrome, Sotos syndrome, and Simpson-Golabi-Behmel syndrome, among others. Race and ethnicity are other genetic factors that influence birth weight. Maternal risk factors for LGA at birth are well documented; independent risk factors include maternal diabetes status during pregnancy, maternal pregestational body weight, and gestational excessive maternal weight gain.¹² Macrosomia is common in diabetic pregnancies, especially in poorly controlled maternal diabetes. The incidence of macrosomia might be higher in infants of pregestational diabetic mothers.

Macrosomia in diabetic mothers is associated with disproportionate body composition resulting in increased ponderal index, excessive body fat, and thicker upper extremity skinfolds compared with nondiabetic infants of similar body size.^{13,14} Whereas insulin-treated diabetes in mothers might be associated with markedly increased risk for LGA and preterm birth, obesity and T2DM in mothers

were associated with mild to moderately increased risk.¹⁵

Both pregestational maternal obesity and excessive gestational maternal weight gain are risk factors for fetal macrosomia.¹⁶ In several studies, degree of pre-pregnancy body weight was shown to have a positive association with birth weight.^{16,17} This relationship is independent of the increased prevalence of gestational diabetes in obese women. Maternal obesity during pregnancy is of particular concern because fetal exposure to in utero nutritional excess and development in an obesogenic environment can cause changes in fetal metabolic programming, leading to long-term adverse health outcomes in adult life (according to the Barker hypothesis).^{6,18} However, shared genetic or familial lifestyle also plays a role.¹⁹

The amount of gestational weight gain associated with LGA birth depends on the body mass index (BMI) of the mother. Guidelines for appropriated levels of gestational weight gain have been released worldwide.²⁰

LGA AND OBESITY

Birth weight is associated with body adiposity throughout an individual's life.²¹ In several previous studies, being born LGA was a predictor of obesity in adulthood.^{22,23} The association between LGA and obesity is summarized in Table 1. The association between birth

Table 1. Literature review for risk of obesity in LGA at birth

Study (year)	Study population	Age affected	Research method	Result
Eriksson et al. (2001) ²⁴	3,847	Adulthood	Cohort study	Incidence of adult obesity increased with increasing birth weight and ponderal index (birthweight/length ³ [birth weight/length ³]; $P=0.01$ and $P=0.04$, respectively). The associations were statistically significant only among males.
Gunnarsdottir et al. (2004) ²⁵	1,874	Adulthood	Cohort study	Birth weight was positively associated with adult BMI in both genders. However, high birth weight was not a risk factor for adult obesity (BMI ≥ 30 kg/m ²).
Johannsson et al. (2006) ²⁶	934	Childhood	Cohort study	Children that weighed above the 85th percentile at birth were more likely than other children to be overweight at the age of 6 years (OR, 1.8), 9 years (OR, 2.1), and 15 years (OR, 2.0).
Gu et al. (2012) ²⁷	5,837	Childhood	Cohort study	Macrosomia infants had a 1.52-fold and 1.50-fold risk, respectively, of being overweight or obese at the age of 7 years ($P=0.001$ and $P=0.000$, respectively).
Schellong et al. (2012) ²⁸	643,902	1–75 yr	Systemic review	High birth weight (>4,000 g) was associated with increased risk of overweight (OR, 1.66; 95% CI, 1.55–1.77).
Eriksen et al. (2015) ²³	348,800	Young adulthood	Cohort study	A positive association existed between birth weight and odds of overweight in young Norwegian males born at term.
Kaul et al. (2019) ²⁹	81,226	Early childhood	Cohort study	LGA is a stronger marker for risk of overweight/obesity in early childhood compared with maternal diabetes during pregnancy. Rate of overweight/obesity in childhood was highest in LGA children born to mothers with gestational diabetes or pre-existing type 2 diabetes mellitus.
Derraik et al. (2020) ³⁰	195,936	Adulthood	Cohort study	Swedish females born LGA based on weight or ponderal index had increased risk of obesity in adulthood, irrespective of birth length.

LGA, large for gestational age; BMI, body mass index; OR, odds ratio; CI, confidence interval.

weight and obesity later in life does not fit a linear, J-, or U-shaped relationship.^{28,31} In one meta-analysis, high birth weight (> 4,000 g) was associated with increased risk of later overweight status in a random effects model (odds ratio [OR], 1.66; 95% confidence interval [CI], 1.55–1.77) as well as in a fixed effects model (OR, 1.61; 95% CI, 1.57–1.65), indicating a linear pattern, except for those with birth weight less than 1,500 g.²⁸ Yu et al.¹⁰ reported that high birth weight (> 4,000 g) was associated with increased risk of obesity (OR, 2.07; 95% CI, 1.91–2.24) compared with subjects with a birth weight < 4,000 g. According to a tracking cohort study, children that weighed above the 85th percentile at birth were more likely to be overweight at the age of 6 years (OR, 1.8), 9 years (OR, 2.1), and 15 years (OR, 2.0) compared to other children.²⁶ In a large Chinese study, an increased predisposition to overweight or obesity at the beginning of childhood was found among macrosomic infants.²⁷ Although birth weight has been positively correlated with adult BMI,²⁴ an association with adult obesity (BMI \geq 30 kg/m²) was not found in one study.²⁵ High birth weight criteria varied by study and subjects, complicating direct comparison of these studies.

LGA based on length is more likely to be genetic and not associated with increased risk of obesity in the long-term.³⁰ Both LGA and maternal diabetes during pregnancy are associated with increased risk of the offspring being overweight/obese in early childhood.³² In a previous study, the rate of childhood obesity was highest (42.9%) in LGA children born to mothers with gestational diabetes or pre-

existing T2DM compared with other groups (no maternal diabetes/appropriate for gestation age (AGA), maternal gestational diabetes/AGA, pre-existing maternal diabetes/AGA, no maternal diabetes/LGA).²⁹ LGA infants have increased risk of becoming overweight or obese children, adolescents, and young adults and have increased risk of birthing LGA offspring (Fig. 1).

PATHOPHYSIOLOGY OF OBESITY IN LGA

The relevant mechanism of obesity in LGA remains unclear. Genetic factors, intrauterine environment, and postnatal environment likely act in combination. Maternal overnutrition promotes hyperglycemia and hyperinsulinemia in the fetus, which lead to excessive fetal adiposity.¹⁰ This extra fat accumulation during fetal life can continue after birth, resulting in obesity. Unlike in LGA, the SGA fetus in response to a suboptimal environment undergoes metabolic adaptations to maximize chances of survival in conditions of ongoing deprivation.³¹ If the postnatal environment provides plentiful nutrition, then these individuals will be at increased risk of obesity as a result of early programming.³¹

High birth weight could increase the levels of growth factors such as insulin and insulin-like growth factors I and II in utero, which can contribute to increased subsequent risk for obesity.³³ LGA is accompanied by a specific pattern change in DNA methylation, including cardiovascular disease candidate genes like apolipoprotein B.³⁴ Early adiposity rebound, which is reported in around 30% of LGA, can play a critical role in childhood obesity in LGA subjects.^{35,36}

LGA AND BODY COMPOSITION

The association between birth weight and fat distribution is important as a possible mediator of obesity-related diseases. Birth weight has shown a positive correlation with lean body mass in children and adults, with high BMI but fat-free body weight.^{37,38} Birth weight is positively associated with adult BMI; however, birth weight has been inversely associated with truncal and abdominal fatness in both adolescence and adult life.^{39,40} The inverse association between birth weight and truncal fat in adulthood indicates impacts of fetal development on adult fat distribution.²⁵

In a recent cohort study, higher birth weight was associated with

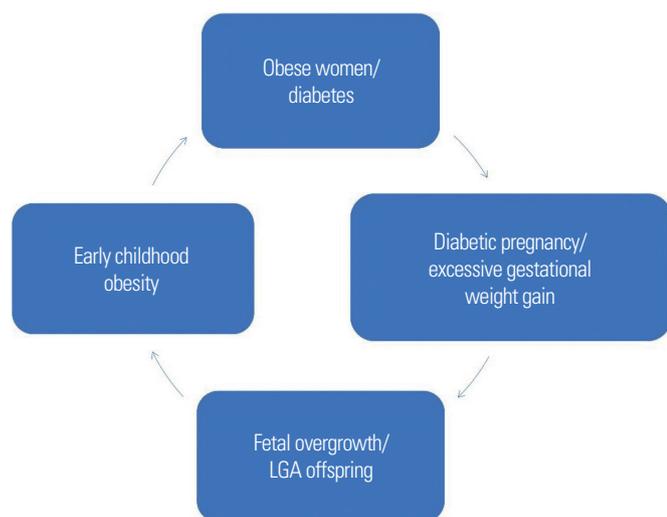


Figure 1. Cycle between large for gestational age (LGA) and obesity.

higher amounts of both lean mass and fat mass.^{41,42} In a Korean study,⁴³ higher birth weight was associated with higher fat mass in adolescents but not with lean mass, a difference that might be due to ethnic differences. Infants born LGA to mothers with diabetes had excess adiposity at birth; infants born LGA to mothers without diabetes mellitus tended to become muscular.⁴⁴ Thus, maternal diabetes and genetic factors can affect body composition of LGA infants.

Furthermore, in several studies, the associations of birth weight with obesity and body composition did not differ based on sex.^{38,42} However, a strong association can exist between birth weight and body fat in adolescent girls, perhaps due to sex steroid hormones and other body composition factors during puberty.⁴³

LGA AND METABOLIC SYNDROME IN CHILDREN AND ADOLESCENTS

The association between LGA and metabolic syndrome is shown in Table 2. Almost all data showed increasing prevalence of metabolic syndrome in LGA subjects, although the research method and expression differed.^{36,45-51}

Similar to SGA, associations among individual components of metabolic syndrome have been observed in LGA subjects. In previous studies, a U-shaped association was found between fasting

insulin level and birth weight.^{52,53} Fasting glucose level and homeostatic model assessment for insulin resistance were significantly higher in normal-weight LGA children compared with normal-weight AGA children.⁵⁴ Furthermore, fasting insulin level was significantly higher in obese LGA children than obese AGA children.⁵⁴ Spiegel et al.⁵⁵ showed that birth weight was not a statistically significant risk factor for developing diabetes mellitus during childhood. In contrast, Wei et al.⁵⁶ suggested that LGA infants are at increased risk of T2DM at school age.

LGA is associated with increased systolic blood pressure during childhood, although evidence regarding the association of LGA and cardiovascular risk factors is limited.^{57,58} In a meta-analysis, birth weight was associated with risk of T2DM and cardiovascular disease in a J-shaped manner but was inversely associated with risk of hypertension.⁵⁹ According to Wang et al.,³⁶ the prevalence of hypertension and hyperlipidemia with high triglyceride level was higher in the LGA obese group than in AGA obese group.

LGA in the absence of maternal diabetes or obesity can result in high BMI during adolescence, which has not been shown to be associated with truncal obesity, insulin resistance, or greater risk of future metabolic disease.⁶⁰ In addition, LGA in the absence of maternal diabetes has been suggested to be a risk factor for insulin resistance during childhood.⁶¹

Table 2. Literature review for risk of metabolic syndrome in LGA at birth

Study (year)	Study population	Age affected	Research method	Result
Boney et al. (2005) ⁴⁵	179	Childhood, adolescence	Cohort study	Children who were LGA at birth had a 2-fold increased risk of metabolic syndrome by 11 years of age (hazard ratio, 2.19; 95% CI, 1.25–3.82). Children who were LGA at birth and exposed to an intrauterine environment of either diabetes or maternal obesity were at increased risk of developing metabolic syndrome.
Wang et al. (2007) ³⁶	372	Childhood	Cross-sectional study	LGA status increased the risk of metabolic syndrome, with hazard ratio of 2.53 (95% CI, 1.42–4.51) in obese children.
Kelishadi et al. (2008) ⁴⁶	4,811	Childhood, adolescence	Cross-sectional study	Birth weight > 4,000 g in boys and < 2,500 g in girls increased the risk of metabolic syndrome (OR, 1.4; 95% CI, 1.01–2.05 and OR, 1.2; 95% CI, 1.1–1.4, respectively).
Guerrero-Romero et al. (2010) ⁴⁷	1,262	Childhood, adolescence	Cross-sectional study	High birth weight (OR, 1.4; 95% CI, 1.2–10.9) was significantly associated with metabolic syndrome in children and adolescents.
Eyzaguirre et al. (2012) ⁴⁸	1,002	Childhood, adolescence	Cross-sectional study	LGA infants were at higher risk of metabolic syndrome than were AGA infants among overweight and obese children and adolescents, by 8.3% and 5.6%, respectively.
Harville et al. (2012) ⁴⁹	2,078	Childhood, young adulthood	Cross-sectional study	High birth weight for gestational age was associated with reduced risk of metabolic syndrome in those with low BMI but not in those with high BMI.
González-Jiménez et al. (2015) ⁵⁰	976	Childhood, adolescence	Cross-sectional study	Infants born with a higher than average birth weight had a greater risk of developing metabolic syndrome in childhood and adolescence.
Romero-Velarde et al. (2016) ⁵¹	120	Childhood, adolescence	Cross-sectional study	Presence of metabolic syndrome was associated with a history of large birth weight (OR, 2.21; range, 1.01–4.82) in children and adolescents with obesity.

LGA, large for gestational age; CI, confidence interval; OR, odds ratio; AGA, appropriate for gestation age; BMI, body mass index.

CATCH-DOWN GROWTH OF LGA INFANTS

Reports regarding growth outcomes among LGA infants are scarce. LGA newborns generally have greater adiposity than AGA newborns.⁶² Most LGA infants show a decelerated growth pattern for weight and length (catch-down growth) in early life,⁶³ physiologically returning to their genetically determined growth trajectories after escaping maternal influence.² The proportion and timing of catch-down growth have not been studied fully. LGA children without catch-down growth show higher subcutaneous fat mass and BMI.⁶⁴ Bueno et al.⁶⁵ reported that catch-down growth in LGA infants was associated with lower BMI and lower abdominal circumference at 25 years compared to those in infants who experienced overgrowth.

Despite catch-down growth, children born LGA have persistently higher weight until the age of 4 years.⁶⁴ In some reports, greater central adiposity was observed at 12 months of age in LGA than in AGA infants.⁶⁶ Vohr and McGarvey⁶⁷ showed a distinct pattern of adiposity, higher BMI, abdominal circumference, and abdominal skinfolds at birth and at 12 months in LGA neonates with diabetic mothers compared with LGA neonates with healthy mothers and AGA neonates with diabetic mothers. LGA due to a diabetic mother or gestational diabetes mellitus should be differentiated from LGA in a healthy mother. Similar to SGA, LGA status with rapid weight gain in childhood is associated with cardiometabolic risk later in life.⁶⁸

CONCLUSION

Pregnant women who have risk factors such as maternal diabetes, pregestational obesity, or excessive gestational weight gain are at high risk of giving birth to LGA neonates. LGA infants are subsequently at increased risk of becoming overweight or obese children, adolescents, and young adults and have increased risk of metabolic syndrome later in life and giving birth to LGA offspring. Education and intervention for weight control before and during pregnancy are necessary to prevent LGA births. Particular attention should be given to diabetic and obese women of reproductive age. Accurate, frequent monitoring of growth in LGA infants and children and early intervention against obesity are necessary. LGA and

the fetal origins of cardiovascular and metabolic disease should be further investigated. In addition, studies are needed to determine whether a difference in occurrence of obesity and metabolic syndrome depends on LGA weight and age affected.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: JEL; acquisition of data: all authors; analysis and interpretation of data: all authors; drafting of the manuscript: YHH; critical revision of the manuscript: JEL; administrative, technical, and material support: YHH; study supervision: JEL.

REFERENCES

1. Bocca-Tjeertes IF, Kerstjens JM, Reijneveld SA, Veldman K, Bos AF, de Winte AF. Growth patterns of large for gestational age children up to age 4 years. *Pediatrics* 2014;133:e643-9.
2. Chiavaroli V, Derraik JG, Hofman PL, Cutfield WS. Born large for gestational age: bigger is not always better. *J Pediatr* 2016; 170:307-11.
3. Koyanagi A, Zhang J, Dagvadorj A, Hirayama F, Shibuya K, Souza JP, et al. Macrosomia in 23 developing countries: an analysis of a multicountry, facility-based, cross-sectional survey. *Lancet* 2013;381:476-83.
4. Palatianou ME, Simos YV, Andronikou SK, Kiortsis DN. Long-term metabolic effects of high birth weight: a critical review of the literature. *Horm Metab Res* 2014;46:911-20.
5. Hong YH, Chung S. Small for gestational age and obesity related comorbidities. *Ann Pediatr Endocrinol Metab* 2018;23: 4-8.
6. Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM. Type 2 (non- insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 1993;36:62-7.
7. Moldéus K, Cheng YW, Wikström AK, Stephansson O. Induction of labor versus expectant management of large-for-

- gestational-age infants in nulliparous women. *PLoS One* 2017; 12:e0180748.
8. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, et al. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991;303:1019-22.
 9. Johnsson IW, Haglund B, Ahlsson F, Gustafsson J. A high birth weight is associated with increased risk of type 2 diabetes and obesity. *Pediatr Obes* 2015;10:77-83.
 10. Yu ZB, Han SP, Zhu GZ, Zhu C, Wang XJ, Cao XG, et al. Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. *Obes Rev* 2011;12:525-42.
 11. Tian JY, Cheng Q, Song XM, Li G, Jiang GX, Gu YY, et al. Birth weight and risk of type 2 diabetes, abdominal obesity and hypertension among Chinese adults. *Eur J Endocrinol* 2006;155:601-7.
 12. Kim SY, Sharma AJ, Sappenfield W, Wilson HG, Salihu HM. Association of maternal body mass index, excessive weight gain, and gestational diabetes mellitus with large-for-gestational-age births. *Obstet Gynecol* 2014;123:737-44.
 13. Persson M, Pasupathy D, Hanson U, Norman M. Birth size distribution in 3,705 infants born to mothers with type 1 diabetes: a population-based study. *Diabetes Care* 2011;34: 1145-9.
 14. Persson M, Fadl H, Hanson U, Pasupathy D. Disproportionate body composition and neonatal outcome in offspring of mothers with and without gestational diabetes mellitus. *Diabetes Care* 2013;36:3543-8.
 15. Kong L, Nilsson IAK, Gissler M, Lavebratt C. Associations of maternal diabetes and body mass index with offspring birth weight and prematurity. *JAMA Pediatr* 2019;173:371-8.
 16. Johnson JW, Longmate JA, Frentzen B. Excessive maternal weight and pregnancy outcome. *Am J Obstet Gynecol* 1992; 167:353-70.
 17. Frentzen BH, Dimperio DL, Cruz AC. Maternal weight gain: effect on infant birth weight among overweight and average-weight low-income women. *Am J Obstet Gynecol* 1988;159: 1114-7.
 18. Reynolds RM, Allan KM, Raja EA, Bhattacharya S, McNeill G, Hannaford PC, et al. Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. *BMJ* 2013;347: f4539.
 19. O'Reilly JR, Reynolds RM. The risk of maternal obesity to the long-term health of the offspring. *Clin Endocrinol (Oxf)* 2013;78:9-16.
 20. Alavi N, Haley S, Chow K, McDonald SD. Comparison of national gestational weight gain guidelines and energy intake recommendations. *Obes Rev* 2013;14:68-85.
 21. Ekelund U, Ong K, Linné Y, Neovius M, Brage S, Dunger DB, et al. Upward weight percentile crossing in infancy and early childhood independently predicts fat mass in young adults: the Stockholm Weight Development Study (SWEDES). *Am J Clin Nutr* 2006;83:324-30.
 22. Cnattingius S, Villamor E, Lagerros YT, Wikström AK, Granath F. High birth weight and obesity: a vicious circle across generations. *Int J Obes (Lond)* 2012;36:1320-4.
 23. Eriksen W, Sundet JM, Tambs K. Birth weight and the risk of overweight in young men born at term. *Am J Hum Biol* 2015; 27:564-9.
 24. Eriksson J, Forsén T, Tuomilehto J, Osmond C, Barker D. Size at birth, childhood growth and obesity in adult life. *Int J Obes Relat Metab Disord* 2001;25:735-40.
 25. Gunnarsdottir I, Birgisdottir BE, Benediktsson R, Gudnason V, Thorsdottir I. Association between size at birth, truncal fat and obesity in adult life and its contribution to blood pressure and coronary heart disease; study in a high birth weight population. *Eur J Clin Nutr* 2004;58:812-8.
 26. Johannsson E, Arngrimsson SA, Thorsdottir I, Sveinsson T. Tracking of overweight from early childhood to adolescence in cohorts born 1988 and 1994: overweight in a high birth weight population. *Int J Obes (Lond)* 2006;30:1265-71.
 27. Gu S, An X, Fang L, Zhang X, Zhang C, Wang J, et al. Risk factors and long-term health consequences of macrosomia: a prospective study in Jiangsu Province, China. *J Biomed Res* 2012;26:235-40.
 28. Schellong K, Schulz S, Harder T, Plagemann A. 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* 2012;7:e47776.
 29. Kaul P, Bowker SL, Savu A, Yeung RO, Donovan LE, Ryan

- EA. Association between maternal diabetes, being large for gestational age and breast-feeding on being overweight or obese in childhood. *Diabetologia* 2019;62:249-58.
30. Derraik JG, Maessen SE, Gibbins JD, Cutfield WS, Lundgren M, Ahlsson F. Large-for-gestational-age phenotypes and obesity risk in adulthood: a study of 195,936 women. *Sci Rep* 2020;10:2157.
 31. Cottrell EC, Ozanne SE. Early life programming of obesity and metabolic disease. *Physiol Behav* 2008;94:17-28.
 32. Xie C, Wang Y, Li X, Wen X. Childhood growth trajectories of etiological subgroups of large for gestational age newborns. *J Pediatr* 2016;170:60-6.e1-5.
 33. Wheatcroft SB, Kearney MT, Shah AM, Ezzat VA, Miell JR, MODO M, et al. IGF-binding protein-2 protects against the development of obesity and insulin resistance. *Diabetes* 2007;56:285-94.
 34. Lin XH, Wu DD, Gao L, Zhang JY, Pan HT, Wang H, et al. Altered DNA methylation in neonates born large-for-gestational-age is associated with cardiometabolic risk in children. *Oncotarget* 2016;7:86511-21.
 35. Whitaker RC, Pepe MS, Wright JA, Seidel KD, Dietz WH. Early adiposity rebound and the risk of adult obesity. *Pediatrics* 1998;101:E5.
 36. Wang X, Liang L, Junfen FU, Lihong DU. Metabolic syndrome in obese children born large for gestational age. *Indian J Pediatr* 2007;74:561-5.
 37. Kahn HS, Narayan KM, Williamson DF, Valdez R. Relation of birth weight to lean and fat thigh tissue in young men. *Int J Obes Relat Metab Disord* 2000;24:667-72.
 38. Singhal A, Wells J, Cole TJ, Fewtrell M, Lucas A. Programming of lean body mass: a link between birth weight, obesity, and cardiovascular disease? *Am J Clin Nutr* 2003;77:726-30.
 39. Barker M, Robinson S, Osmond C, Barker DJ. Birth weight and body fat distribution in adolescent girls. *Arch Dis Child* 1997;77:381-3.
 40. Byberg L, McKeigue PM, Zethelius B, Lithell HO. Birth weight and the insulin resistance syndrome: association of low birth weight with truncal obesity and raised plasminogen activator inhibitor-1 but not with abdominal obesity or plasma lipid disturbances. *Diabetologia* 2000;43:54-60.
 41. Perng W, Hajj H, Belfort MB, Rifas-Shiman SL, Kramer MS, Gillman MW, et al. Birth size, early life weight gain, and mid-childhood cardiometabolic health. *J Pediatr* 2016;173:122-30.
 42. Liu J, Au Yeung SL, He B, Kwok MK, Leung GM, Schooling CM. The effect of birth weight on body composition: evidence from a birth cohort and a Mendelian randomization study. *PLoS One* 2019;14:e0222141.
 43. Kang M, Yoo JE, Kim K, Choi S, Park SM. Associations between birth weight, obesity, fat mass and lean mass in Korean adolescents: the Fifth Korea National Health and Nutrition Examination Survey. *BMJ Open* 2018;8:e018039.
 44. de Zegher F, Pérez-Cruz M, Sebastiani G, Díaz M, López-Bermejo A, Ibáñez L. Large for gestational age newborns from mothers without diabetes mellitus tend to become tall and lean toddlers. *J Pediatr* 2016;178:278-80.
 45. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics* 2005;115:e290-6.
 46. Kelishadi R, Gouya MM, Adeli K, Ardalan G, Gheiratmand R, Majdzadeh R, et al. Factors associated with the metabolic syndrome in a national sample of youths: CASPIAN Study. *Nutr Metab Cardiovasc Dis* 2008;18:461-70.
 47. Guerrero-Romero F, Aradillas-García C, Simental-Mendía LE, Monreal-Escalante E, de la Cruz Mendoza E, Rodríguez-Moran M. Birth weight, family history of diabetes, and metabolic syndrome in children and adolescents. *J Pediatr* 2010;156:719-23.
 48. Eyzaguirre F, Bancalari R, Román R, Silva R, Youlton R, Urquidí C, et al. Prevalence of components of the metabolic syndrome according to birthweight among overweight and obese children and adolescents. *J Pediatr Endocrinol Metab* 2012;25:51-6.
 49. Harville EW, Srinivasan S, Chen W, Berenson GS. Is the metabolic syndrome a “small baby” syndrome?: the bogalusa heart study. *Metab Syndr Relat Disord* 2012;10:413-21.
 50. González-Jiménez E, Montero-Alonso MA, Schmidt-RioValle J, García-García CJ, Padez C. Metabolic syndrome in Spanish adolescents and its association with birth weight, breastfeeding duration, maternal smoking, and maternal obesity: a cross-sectional study. *Eur J Nutr* 2015;54:589-97.

51. Romero-Velarde E, Aguirre-Salas LM, Álvarez-Román YA, Vásquez-Garibay EM, Casillas-Toral E, Fonseca-Reyes S. Prevalence of metabolic syndrome and associated factors in children and adolescents with obesity. *Rev Med Inst Mex Seguro Soc* 2016;54:568-75.
52. Murtaugh MA, Jacobs DR Jr, Moran A, Steinberger J, Sinaiko AR. Relation of birth weight to fasting insulin, insulin resistance, and body size in adolescence. *Diabetes Care* 2003;26:187-92.
53. Dabelea D, Pettitt DJ, Hanson RL, Imperatore G, Bennett PH, Knowler WC. Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults. *Diabetes Care* 1999;22:944-50.
54. Chiavaroli V, Giannini C, D'Adamo E, de Giorgis T, Chiarelli F, Mohn A. Insulin resistance and oxidative stress in children born small and large for gestational age. *Pediatrics* 2009;124:695-702.
55. Spiegel E, Shoham-Vardi I, Sergienko R, Landau D, Sheiner E. The association between birth weight at term and long-term endocrine morbidity of the offspring. *J Matern Fetal Neonatal Med* 2019;32:2657-61.
56. Wei JN, Sung FC, Li CY, Chang CH, Lin RS, Lin CC, et al. Low birth weight and high birth weight infants are both at an increased risk to have type 2 diabetes among schoolchildren in Taiwan. *Diabetes Care* 2003;26:343-8.
57. Zhang Y, Li H, Liu SJ, Fu GJ, Zhao Y, Xie YJ, et al. The associations of high birth weight with blood pressure and hypertension in later life: a systematic review and meta-analysis. *Hypertens Res* 2013;36:725-35.
58. Skilton MR, Siitonen N, Würtz P, Viikari JS, Juonala M, Sepälä I, et al. High birth weight is associated with obesity and increased carotid wall thickness in young adults: the cardiovascular risk in young Finns study. *Arterioscler Thromb Vasc Biol* 2014;34:1064-8.
59. Knop MR, Geng TT, Gorny AW, Ding R, Li C, Ley SH, et al. Birth weight and risk of type 2 diabetes mellitus, cardiovascular disease, and hypertension in adults: a meta-analysis of 7 646 267 participants from 135 studies. *J Am Heart Assoc* 2018;7:e008870.
60. Bouhours-Nouet N, Dufresne S, de Casson FB, Mathieu E, Douay O, Gatelais F, et al. High birth weight and early postnatal weight gain protect obese children and adolescents from truncal adiposity and insulin resistance: metabolically healthy but obese subjects? *Diabetes Care* 2008;31:1031-6.
61. Evagelidou EN, Kiortsis DN, Bairaktari ET, Giapros VI, Cholevas VK, Tzallas CS, et al. Lipid profile, glucose homeostasis, blood pressure, and obesity-anthropometric markers in macrosomic offspring of nondiabetic mothers. *Diabetes Care* 2006;29:1197-201.
62. Schmelzle HR, Quang DN, Fusch G, Fusch C. Birth weight categorization according to gestational age does not reflect percentage body fat in term and preterm newborns. *Eur J Pediatr* 2007;166:161-7.
63. Chiavaroli V, Cutfield WS, Derraik JG, Pan Z, Ngo S, Sheppard A, et al. Infants born large-for-gestational-age display slower growth in early infancy, but no epigenetic changes at birth. *Sci Rep* 2015;5:14540.
64. Taal HR, Vd Heijden AJ, Steegers EA, Hofman A, Jaddoe VW. Small and large size for gestational age at birth, infant growth, and childhood overweight. *Obesity (Silver Spring)* 2013;21:1261-8.
65. Bueno AC, Espiñeira AR, Fernandes-Rosa FL, de Souza RM, de Castro M, Moreira AC, et al. Adiponectin: serum levels, promoter polymorphism, and associations with birth size and cardiometabolic outcome in young adults born large for gestational age. *Eur J Endocrinol* 2010;162:53-60.
66. Moschonis G, Grammatikaki E, Manios Y. Perinatal predictors of overweight at infancy and preschool childhood: the GENESIS study. *Int J Obes (Lond)* 2008;32:39-47.
67. Vohr BR, McGarvey ST. Growth patterns of large-for-gestational-age and appropriate-for-gestational-age infants of gestational diabetic mothers and control mothers at age 1 year. *Diabetes Care* 1997;20:1066-72.
68. Lurbe E, Garcia-Vicent C, Torro MI, Aguilar F, Redon J. Associations of birth weight and postnatal weight gain with cardiometabolic risk parameters at 5 years of age. *Hypertension* 2014;63:1326-32.