

SUPPLEMENT ARTICLE

Low birth weight and small for gestational age are associated with complications of childhood and adolescence obesity: Systematic review and meta-analysis

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Funding information

European Regional Development Fund; Instituto de Salud Carlos III; Horizon 2020 Framework Programme, Grant/Award Number: 774548

Summary

In recent decades, the incidence of type 2 diabetes (T2D) has increased dramatically in children and adolescents, posing a real public health problem. Beyond unhealthy diets and sedentary lifestyles, growing evidence suggests that some perinatal factors, such as low birth weight (LBW), are associated with higher risk of T2D in adulthood. In this regard, it remains unclear whether the increased risk is already present in childhood and adolescence. We conducted a systematic review and meta-analysis to clarify the association of LBW or being small for gestational age (SGA) with insulin resistance in childhood and adolescence. The systematic review resulted in 28 individual studies, and those with the same outcome were included within two random-effects meta-analyses. Compared with children or adolescents born with adequate size for gestational age, those SGA had 2.33-fold higher risk of T2D (95% confidence interval [CI]: 1.05–5.17). Furthermore, LBW and being SGA were associated with 0.20 higher mean homeostasis model assessment of insulin resistance (HOMA-IR) values (95% CI: 0.02–0.38). Given the high prevalence of preterm babies, from a population perspective, these results may be of great importance as they point to the existence of a potentially vulnerable subgroup of children and adolescents that could benefit from screening tests and early preventive strategies.

KEYWORDS

insulin resistance, low birth weight, small for gestational age, STOP project

Abbreviations: AGA, adequate for gestational age; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; LBW, low birth weight; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; SGA, small for gestational age; T2D, type 2 diabetes.

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1 | INTRODUCTION

Similar to other chronic diseases, the prevalence of type 2 diabetes (T2D), typically diagnosed in adults and elder populations, has increased dramatically in children and adolescents in the last two decades.¹ Global data concerning both its incidence and prevalence indicate large differences among countries depending on ethnicity

and geographical region. The incidence of T2D in children and adolescents ranges from 0 to 330 per 100,000 persons/year and the prevalence from 0 to 5300 per 100,000 persons worldwide.² Populations containing Native American, Hispanic, Black, and southern Asian ethnic backgrounds report the highest rates; meanwhile, Europe shows the lowest rates.³

Given the increasing incidence and prevalence in children and adolescents, T2D may become a public health issue that affects both developed and developing countries.¹ Therefore, from a population perspective, it is important to identify potential risk factors and define those vulnerable groups of individuals that may benefit from screening and preventive strategies.

In addition to genetics and unhealthy lifestyle (unbalanced diets and sedentarism), early life exposures have been postulated as potential risk factors for the development of chronic and noncommunicable diseases.^{4,5} In this context, recent evidence has suggested that birth weight, an indicator of the intrauterine environment, may be particularly important for the development of future diseases, such as diabetes.⁶ In 2012, 23.3 million babies were born small for gestational age (SGA) in low- and middle-income countries.⁷ Among them, 11.2 million were born at term and with adequate birth weight (≥ 2500 g), 10.7 million were born at term, but with low birth weight (LBW) (< 2500 g), and 1.5 million were born preterm.

Two systematic reviews and meta-analyses concluded that birth weight was indirectly associated with the risk of T2D in adulthood.^{6,8} However, evidence in pediatric populations is scarce and inconsistent. Therefore, the aim of the present study was to conduct a systematic review and meta-analysis to clarify the association of birth weight, LBW, and SGA with the risk of insulin resistance and T2D in childhood and adolescence.

2 | MATERIAL AND METHODS

2.1 | Literature and search strategy

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidance.⁹ The protocol of this systematic review was registered in the international prospective register of systematic reviews (PROSPERO ID 166682). Eligible studies were identified by searching electronic bibliography databases (PubMed Central and Web of Science). Search terms used for medical subject headings and key words were as follows: (“infant, small for gestational age” OR “infant, low birth weight”) AND (“diabetes mellitus” OR “insulin resistance”). The PubMed search strategy was as follows: (“infant, small for gestational age”[MeSH] OR “infant, low birth weight”[MeSH]) AND (“diabetes mellitus”[MeSH] OR “insulin resistance”[MeSH]) AND (“2010/01/26”[PDat]: “2020/01/23”[PDat] AND English[lang] AND (“infant”[MeSH Terms] OR “child”[MeSH Terms] OR “adolescent”[MeSH Terms])). Results were limited to articles written in English, published within the last 10 years, and conducted in young populations. The search was last executed on January 26, 2020.

2.2 | Article selection

Two authors (N.M.-C. and L.G.) independently selected the articles, scored their quality, and extracted the data. Disagreement was resolved by discussion. Article screening, quality assessment, and data extraction were developed with an online software for systematic review management (Covidence.org).

Prior to article selection, the eligibility criteria were defined regarding (1) study design (cross-sectional, prospective cohort, retrospective cohort, or case-control study); (2) definition of the exposure (LWB or SGA); (3) definition of the outcome (parameters of insulin resistance, prediabetes, or T2D); (4) study population (from 1 to 18 years old); and (5) publication status (published originals). Reviews (including systematic reviews), meta-analyses, conference abstracts, and gray literature were excluded.

2.3 | Data extraction

The following information was extracted from each study: (1) name of the first author; (2) year of publication; (3) country of study; (4) study design; (5) sample size; (6) special characteristics of the study population; (7) definition of the exposure; (8) definition of the outcome; (9) age at which the outcome was assessed; (10) main results; and (11) control for confounding, including the list of covariates included in the multivariate analyses.

2.4 | Quality assessment

The risk of bias in the included studies was systematically assessed using the Quality Assessment Tool for Observational Cohort and Cross-sectional Studies (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>), which included 14 questions and 3 response options (yes, no, and cannot determine/not applicable/not reported). Item 10 (Was the exposure(s) assessed more than once over time?) was not considered; therefore, the screened index actually contained 13 questions. For each item, the response options scored either +1 or -1 point indicating low risk or high risk of bias, respectively. Finally, we classified the studies as very low (< 0 points), low (0–3 points), medium (4–7 points), high (8–10 points), or very high quality (11–13 points).

2.5 | Statistical analysis

Studies that reported the outcome in a similar manner were included in the meta-analysis. The pooled estimates for fasting serum glucose and insulin were not calculated due to the small number of studies that reported adjusted means and the high heterogeneity found among them. Random effects models were used to estimate (1) pooled hazard ratio (HR) and 95% confidence interval (CI) for T2D and (2) overall mean difference and 95% CI for homeostasis model

assessment of insulin resistance (HOMA-IR). Heterogeneity was assessed with the Q -test and the I^2 statistic, representing the total variation across studies that can be attributed to heterogeneity. p value below 0.05 was considered statistically significant. The statistical analysis was conducted with Stata Version 14 (StataCorp LP, College Station, TX, USA).

3 | RESULTS

The search yielded 1070 items, 68 of which were duplicates. Of the remaining 1002 articles, 950 were excluded based on title and abstract, whereas the remaining 52 were reviewed in full text. Thirty-four articles were excluded because they did not meet the eligibility criteria, leaving a total of 28 articles for inclusion in this review (Figure 1).

Main characteristics of all the included studies are presented in Table S1. Sixteen studies were conducted in European populations (two in France,^{10,11} one in Finland,¹² one in Germany,¹³ two in Greece,^{14,15} one in Italy,¹⁶ one in Portugal,¹⁷ one in Romania,¹⁸ one in Slovakia,¹⁹ one in Spain,²⁰ three in Sweden,²¹⁻²³ one in the Netherlands,²⁴ and one in Turkey²⁵), six in American populations (three in Brazil,²⁶⁻²⁸ two in Mexico,^{29,30} and one in the United States³¹), and six in Asian populations (three in China,³²⁻³⁴ one in Japan,³⁵ one in Korea,³⁶ and one in Taiwan³⁷). Regarding the study designs, we found 17 cross-sectional studies,^{14-19,22,25-27,29,30,32-35,37} 9 prospective cohorts,^{10-13,20,21,23,24,28} 1 retrospective cohort,³⁷ and 1 case-control study.³¹ Seven studies used a matched design.^{12,15,16,21,32,33,37} Ten out of the 28 studies had small sample sizes^{10,11,15,19,20,22,25,30,33,35} (<100 participants), 9 had medium sample sizes^{12,13,16,17,21,24,26,34} (100-500 participants), and another 9 had large sample sizes^{14,18,23,27,28,36,37} (>500 participants).

Most of the studies compared children born SGA, defined as birth weight below 2 standard deviations or the 10th percentile of the local standard of reference, with children born adequate for gestational age (AGA). However, seven studies compared children with LBW, defined as birth weight below 2500 g, with children born with normal (2500-4000 g) birth weight^{26,30,31} and/or high birth weight (over 3400 g³⁵ or 4000 g^{17,27,29}). Participants' age ranged from 2 to 17 years old at the time of outcome assessment. Several studies reported p values adjusted for age,^{16,17} sex,^{10,36} or both.^{12,15,20,28,30,34} Other confounders frequently accounted for were body mass index (BMI)^{15,21,22,28,33-35} and pubertal status.^{15,30,33} Nevertheless, up to 15 studies did not report adjusted results for the outcomes of interest for this review.^{13,15,16,18,19,21,24-27,29,30,32,33,35}

The mean quality score for the 28 included studies was 3 points, ranging from -4 to 10 points. Six of the included studies had very low quality, 14 low quality, 5 medium quality, and 3 high quality. Most of the studies failed to calculate the required sample size for the analyses and consider different levels of exposure (birth weight as both quantitative and qualitative variables, for example). Aside from this, the main sources of bias were primarily related to the cross-sectional design of the studies.

3.1 | Studies reporting the risk of T2D

Three studies assessed the risk of T2D as a dichotomous variable.^{23,31,37} Mokhashi et al.³¹ reported no significant association in a case-control study with 50,337 African Americans. However, a large retrospective cohort study in Taiwan³⁷ and a large prospective cohort study in Sweden²³ reported significantly higher risks of T2D in children and adolescents born SGA than their peers born AGA after

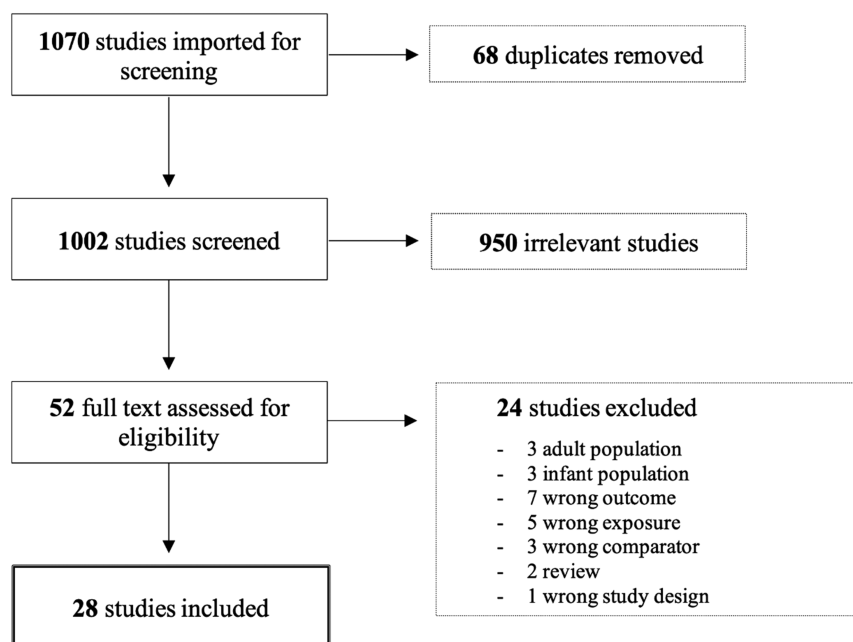


FIGURE 1 Flow diagram of study selection

adjusting for potential confounders. The pooled analysis of the results from these cohorts (Figure S1) showed that compared with AGA children and adolescents, those born SGA had 2.33-fold higher risk of developing T2D (95% CI: 1.05–5.17).

3.2 | Studies reporting mean serum values for fasting glucose, insulin, and HOMA-IR

The most commonly reported outcomes were fasting serum levels of glucose, insulin, and/or HOMA-IR. Studies that presented at least one of these outcomes are summarized in Table 1. Mean levels of fasting serum glucose were reported by 18 studies, of which only 6 found significant differences for SGA versus AGA children^{11,19,21,22,32} or for children with LBW versus high birth weight.²⁹ Blusková et al.¹⁹ and Kistner et al.²² reported significantly higher fasting serum glucose in SGA compared with AGA children aged 3 to 11 years old in unadjusted models, while Guerrero-Romero et al.²⁹ found that, compared with normal birth weight children, those with LBW had significantly higher fasting serum glucose levels. On the contrary, Milovanovic et al.¹¹ found significantly higher levels of fasting serum glucose in AGA compared with SGA children at the age of 4 after adjusting for sex and fat mass, and Liu et al.³² reported similar results comparing SGA children with catch-up growth versus AGA children.

Mean levels of fasting serum insulin or HOMA-IR were reported by 17 and 19 studies, respectively. Compared with AGA children, several studies found significantly higher mean serum fasting insulin,^{33,34} HOMA-IR,²⁸ or both^{15,16} in children born SGA after adjusting for age, sex, BMI, and pubertal status. The opposite was reported by Sebastiani et al.²⁰ who additionally adjusted for type of delivery and breastfeeding. Regarding studies that accounted for catch-up growth, Liu et al.³² reported that SGA children with catch-up growth had significantly lower mean fasting serum insulin and HOMA-IR than children born AGA in crude models. Similarly, Deng et al.³⁴ found that compared with AGA children, those SGA without catch-up growth had lower mean fasting insulin, while those SGA with catch-up growth had higher mean fasting insulin after accounting for age, sex, and BMI.

Regarding birth weight, all the studies reported higher mean levels of both insulin and HOMA-IR in children with LBW compared with their peers with normal birth weight^{27,30} or high birth weight,³⁵ after adjusting for age, sex, and pubertal status. The four studies (five comparisons) that reported adjusted means of HOMA-IR were meta-analyzed (Figure 2). Children or adolescents born SGA or with LBW had significantly higher levels of HOMA-IR than their peers born AGA or with normal birth weight.

3.3 | Other outcomes

Less commonly reported outcomes are shown in Table 2. Those outcomes included continuous variables such as QUICKI,^{10,12} HOMA %, ^{15,32,34} HOMA- β ,³³ HbA1c,²² and qualitative variables, such as high fasting serum glucose (>100 mg/dl),^{19,26,27} insulin (>24.9 mU/ml),¹⁹

or HOMA-IR (>3.16).^{14,19,27} Regarding continuous variables, studies reported that children born SGA had significantly higher mean HOMA %^{15,32} and HOMA- β ³³ than their peers born AGA. Regarding dichotomous variables, Manios et al.¹⁴ reported significantly higher odds for HOMA > 3.16 in children born SGA compared with those born AGA.

4 | DISCUSSION

In this systematic review and meta-analysis, it was evidenced that, compared with children or adolescents born AGA, those born SGA showed higher insulin resistance, measured with the HOMA-IR, and higher risk of T2D. To our knowledge, this is the first systematic review and meta-analysis examining the association between being SGA and the risk of T2D in childhood or adolescence. The lack of evidence in young populations may be due to the low prevalence of T2D in that group. Nevertheless, due to the increasing trends in the prevalence of obesity and obesity-related disorders in childhood and adolescence, our results are of value for implementing public health prevention strategies.

Using the information provided by two large prospective cohorts,^{23,37} we found that children born SGA had 2.33-fold higher risk of T2D in childhood or adolescence (95% CI: 1.05–5.17). In analyses restricted to preterm children, Huang et al.³⁷ also reported higher estimates than Crump et al.²³ (HR: 2.38 [95% CI: 1.87–3.03] vs. HR: 1.26 [95% CI: 1.01–1.58]). The high heterogeneity observed between these studies ($I^2 = 88.3\%$; $p = 0.003$) could be attributed to ethnic differences between the study populations, mean age of participants, and different control for confounding, which was more thorough in the Swedish study. Due to the few studies included in the meta-analysis and the high heterogeneity, we acknowledge that the obtained pool estimate may perhaps represent the upper limit of the true association between being SGA and the risk of T2D.

Moreover, the results of the comparisons for mean levels of serum glucose, insulin, and HOMA-IR are inconsistent, in particular those regarding fasting serum glucose. This discrepancy may be explained, at least partially, by a suboptimal control of confounding, because very few studies reported adjusted means of serum parameters. It should also be noted that not all the parameters for the diagnosis of impaired glucose metabolism are equally sensitive. Also, it is possible that in the early stages of the disease, keeping fasting serum levels of glucose within the limits of normality requires a greater metabolic effort. If this were the case, oral glucose overload tests would be more sensitive than fasting serum glucose for the diagnosis of impaired glucose metabolism at early stages.

Focusing on fasting serum parameters, it was hypothesized that if being SGA was associated with impaired glucose metabolism in childhood and adolescence, the first metabolic change would be related to increased insulin resistance. This observation in turn would be reflected by increased fasting serum insulin and HOMA-IR, leading to a normal mean fasting glucose level. Greater consistency was observed among studies assessing fasting serum insulin and HOMA-

TABLE 1 Description of the studies reporting the main outcomes

Author	Year	Age (years) /population	Comparison groups	Outcome		HOMA-IR	Adjusted
				Glucose (mg/dl)	Insulin (mU/L)		
Oliveira-Santos J. ¹⁷	2019	Girls 14.1 (1.7) Boys 14.0 (1.6)	LBW	90.05 (10.81)	3.53 (1.70)	Age, pubertal stage, BMI, fat mass, socioeconomic status, KIDMED index	No
			NBW	90.05 (9.01)	3.46 (1.66)		
			HBW	84.65 (9.01)	4.53 (1.71)		
			LBW	81.05 (9.01)	3.3 (0.93)		
			NBW	80.9 (9.3)	3.25 (1.19)		
			HBW	80.9 (10.5)	3.36 (1.33)		
Ledo D.L. ²⁷	2018	9.5 (2.0)	LBW	80.9 (9.3)	2.42 (1.97)	No	
			ABW	80.9 (10.5)	1.83 (1.61)		
			HBW	79.3 (8.2)	1.41 (0.68)		
Liu C. ³²	2017	2 3 4	SGA	74.2 (5.76)	1.97 (0.61)	No	
			AGA	78.7 (6.66)	2.88 (0.69)		
			SGA	74.74 (3.96)	2.55 (0.69)		
			AGA	81.23 (4.86)	3.25 (0.96)		
Ranke M.B. ¹³	2016	8.3 (0.7)	SGA	75.28 (5.22)	3.27 (1.03)	No	
			AGA	80.68 (5.76)	3.21 (1.02)		
de Jong M. ^{b, 24}	2015	2	SGA	83 (5.4)	4.75 (2.30)	No	
			AGA	81 (8.2)	5.04 (3.74)		
			VLBW	302 (0.14–27.49)	0.6 (0.02–6.5)		
Dominguez- Hernández C. ³⁰	2015	10.1 (1.8)	SGA	86.85 (8.82)	2.94 (0.14–13.71)	No	
			AGA	88.5 (9.65)	2.58 (0.14–26.08)		
			OB LBW	93.33 (12.75)	14.1 (10.89)		
dos Santos Alves P. de J. ²⁶	2015	13.2 (2.5)	OB NBW	86.85 (8.82)	8.3 (7.19)	No	
			EU NBW	88.5 (9.65)	4.36 (3.12)		
Fulghesu A.M. ¹⁶	2015	17.2 (2.2)	LBW	79.7 (9.6)	15.93 (7.16)	No	
			NBW	82.3 (9.5)	10.97 (5.79)		

(Continues)

TABLE 1 (Continued)

Author	Year	Age (years) /population	Comparison groups	Outcome			Adjusted
				Glucose (mg/dl)	Insulin (mU/L)	HOMA-IR	
Huang Y. ³³	2015	6.5 (2.5)	SGA	84.65 (10.81)	8.1 (4.7)	1.6 (1.0–1.9)	No
			AGA	82.85 (9.01)	3.9 (1.4)	0.8 (0.6–1.0)	
Sebastiani G. ^{c, 20}	2015	3	SGA	84.65 (9.35)		0.3 (0.52)	Age, sex, type of delivery, breastfeeding, BMI
			AGA	81.05 (7.85)		0.1 (0.09)	
			SGA	86.45 (9.35)		0.5 (0.52)	
			AGA	86.45 (7.85)		1 (0.87)	
Blusková Z. ¹⁹	2014	7.2 (7.1)	SGA	83.57 (8.1)	6.24 (5.66)	1.28 (1.13)	No
			AGA	70.6 (9.37)	5.48 (4.55)	0.98 (0.84)	
Cho W.K. ³⁶	2014	14.1 (2.1)	SGA		12.88 (7.76)	2.83 (2.00)	Birth weight
			AGA		13.47 (8.56)	2.98 (1.76)	
Milovanovic I. ¹¹	2014	4	SGA	75.64 (14.41)	2.4 (1.5)		Fat mass, sex
			AGA	82.85 (9.01)	3 (1.7)		
Stroescu R. ¹⁸	2014	Prepubertal	SGA	86.45 (10.81)			No
			AGA	81.95 (9.55)			
		Pubertal	SGA	83.75 (9.55)			
			AGA	81.95 (12.79)			
		Adolescents	SGA	79.24 (3.96)			
			AGA	84.11 (11.35)			
Uçar A. ^{b, 25}	2014	6.8 (0.6)	SGA	78.8 (9.9)	7.0 (5.6–9.2)	2.3 (2.1–2.4)	No
			AGA	80.2 (7.4)	10.2 (9.0–11.5)	2.5 (2.4–2.6)	
Giapros V.I. ¹⁵	2013	6.1 (1.3)	SGA	80.2 (9.2)	6.35 (3.4)	1.34 (0.67)	No
			AGA	82.3 (6.5)	4.62 (2.21)	0.99 (0.53)	
Kistner A. ^{d, 22}	2012	9.9 (8.5–10)	SGA	79.24 (11.53)	6 (3.26)	1.19 (0.66)	Insulin and HOMA-IR adjusted for BMI
			AGA	73.84 (9.91)	4.3 (2.25)	0.78 (0.47)	
Milovanovic I. ¹⁰	2012	2	SGA	81.05 (5.4)	2 (1.6)		Sex, fat mass
			AGA	81.05 (14.41)	2 (1.5)		
Mori M. ³⁵	2012	15.4 (1.4)	LBW	90.5 (9.1)	17.2 (13)	4 (3.6)	No
			HBW	91.1 (7.5)	11.2 (6.2)	2.5 (1.4)	
Deng H.Z. ^{c, 34}	2011	6.6 (3.3)	CUG SGA	82.85 (0)	9.3 (13.1)	1.2 (0.2–13.6)	Sex, age, current BMI
			NCUG SGA	79.24 (10.9)	3.7 (3.04)	0.5 (0.0–3.2)	
			AGA	84.65 (11.6)	5.4 (2.59)	2.4 (0.2–2.6)	

TABLE 1 (Continued)

Author	Year	Age (years) /population	Comparison groups	Outcome		Adjusted
				Glucose (mg/dl)	Insulin (mU/L)	
Guerrero-Romero F. ²⁹	2010	11.8 (2.2)	LBW	95.6 (13.2)		No
			NBW	88.5 (11.2)		
			HBW	92.6 (9.8)		
Lemos J.O. ^{6, 28}	2010	6.57 (0.66)	SGA		0.23 (0.03-0.43)	Age, sex, BMI, WC, HDL-c, LDL-c, TAG,
			AGA			per capita income
Tenhola S. ¹²	2010	12.2 (0.2)	SGA		1.91 (0.74)	No
			AGA			2.03 (0.96)

Note: Data are mean (SD).

Abbreviations: ABW, adequate birth weight; AGA, adequate for gestational age; BMI, body mass index; CUG, catch-up growth; EU, eutrophic; HBW, high birth weight; HDL-c, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; KIDMED index, Mediterranean diet quality index for children and adolescents; LBW, low birth weight; LDL, low-density lipoprotein-cholesterol; NBW, normal birth weight; NCUG, non-catch-up growth; OB, obese; SGA, small for gestational age; TAG, triacylglyceride; VLBW, very low birth weight; WC, waist circumference.

^aFor insulin and HOMA-IR, data are median (interquartile range).

^bFor insulin and HOMA-IR, data are median (range).

^cFor HOMA-IR, data are median (range).

^dFor age, data are median (range).

^eFor HOMA-IR, data are beta coefficient (95% confidence interval).

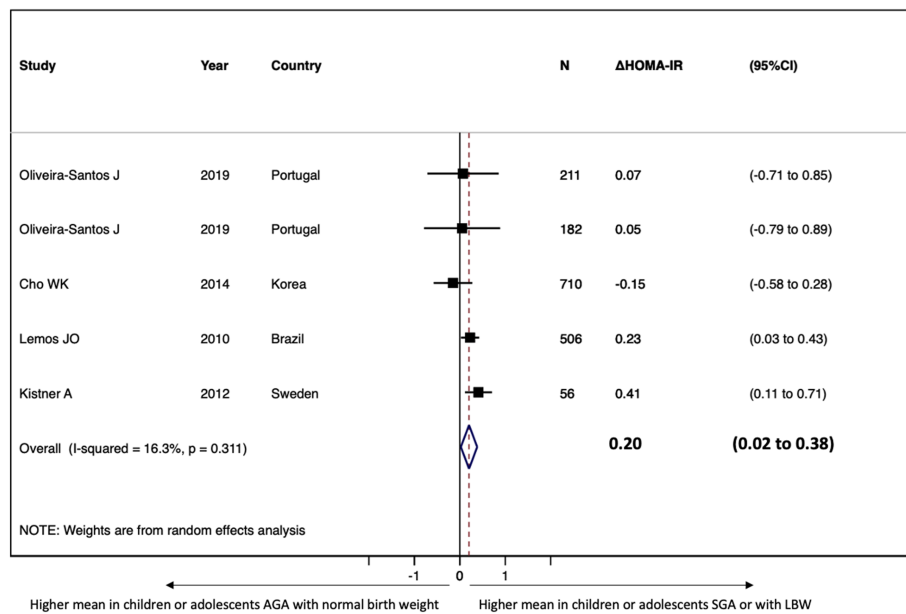


FIGURE 2 Meta-analysis of the association of being small for gestational age or having low birth weight with insulin resistance in childhood or adolescence. Analyses restricted to studies reporting adjusted means

IR, of which the great majority reported higher mean levels of both parameters in SGA^{15,16,28,33,34} or LBW^{27,30,35} children compared with controls. Nevertheless, three studies reported higher mean levels of fasting serum insulin,³⁴ HOMA-IR,²⁰ or both³² in AGA compared with SGA children. Those results may be explained by the study design, inconsistent definition of the exposure,^{32,34} participants' age,^{32,34} and suboptimal control of confounding.³² Sebastiani et al.²⁰ found higher HOMA-IR in AGA compared with SGA children in a multivariable adjusted model at 6 years but not at 3 years, which may suggest a possible interaction with age. The studies by Liu et al.³² and Deng et al.³⁴ are the only ones that included SGA children with catch-up growth in their study sample. Liu et al. compared AGA versus SGA with catch-up children and found significantly higher levels of HOMA-IR and fasting serum insulin in AGA children at 2 and 3 years, but not at 4 years. Although the authors reported using a matched design, information was lacking on the variables used for matching and the result estimates were not adjusted for potential confounders. Deng et al. found significant differences in mean levels of fasting serum insulin comparing AGA, SGA with catch-up and SGA without catch-up children, but did not present two-by-two comparisons. In addition, this same study included children aged between 1.5 and 11.2 years, and although the ANCOVA was adjusted for sex and age, the authors did not present any test for interaction or subgroup analysis. Overall, we found that compared with AGA children, those born SGA had a slight but significantly higher mean HOMA-IR. However, the meta-analysis only included the four studies (five comparisons) that reported adjusted means, and thus, further research is needed to elucidate the real magnitude of the association.

Our findings agree with a systematic review published in 2014 that reported relative inconsistency in the results from studies assessing the association of prematurity or being SGA with insulin sensitivity in childhood and adolescence.³⁸ As previously highlighted, this preexisting systematic review with 26 studies published between 2000 and 2012 also

pointed out the heterogeneity between studies regarding methodology, study population, and definition of the exposure. Although most preterm have LBW, not all infants who have LBW are SGA. Furthermore, not all SGA children will have experienced intrauterine growth restriction and not all infants who suffered intrauterine growth restriction will be SGA. Gestational age, birth weight, and intrauterine growth represent different, but closely related facets of fetal development and, therefore, may be difficult to separate their effects. Moreover, this previous systematic review aimed at outlining the changes seen in insulin sensitivity over the life course. Thus, it investigated cohorts at different ages and presented the results by age group, suggesting that age could be a potential effect modifier.

While evidence in children and adolescents is still building, a recently published systematic review and meta-analysis of 135 studies in adult populations reported birth weight was associated with T2D, cardiovascular disease, and hypertension.⁶ For T2D, the authors found a J-shaped association, indicating the lowest risk among those participants with birth weight between 3500 and 4000 g.

The biological mechanisms underlying the observed association are not fully understood. The fetal programming theory states that metabolic stress in utero may lead to epigenetic changes, abnormal vascularization, and aberrant endocrine regulation, including decrease leptin levels and altered intracellular insulin signaling, that may result in important disruptions to the endocrine system later in life.^{39,40} On the other hand, the early catch-up theory puts greater emphasis on malnutrition during the perinatal period. LBW babies are often overfed, resulting in poor programming of neuroendocrine circuits,⁶ cellular aging, and/or epigenetic mechanisms³⁸ that lead to fast catch-up growth and diabetogenic^{7,41,42} disturbances throughout life.

Catch-up growth is defined as weight gain from birth to 2 years of age over 0.67 standard deviations. Besides overfeeding, there are other factors associated with catch-up growth, including the severity of the LBW, the presence of comorbidities, and the type of feeding. In

TABLE 2 Description of the studies reporting secondary outcomes

Author	Year	Age (years)	Comparison groups	Quantitative outcomes				Qualitative outcomes			
				QUICKI	HOMA %	HOMA- β	HbA1c	Glucose > 100 mg/dl	HOMA-IR > 3.16	Insulin > 24.9 μ U/ml	Adjusted
Ledo D.L. ²⁷	2018	9.5 (2.0)	LBW					1/70	13/70		Sex
			ABW					5/418	46/418		
			HBW					0/30	1/30		
Liu C. ³²	2017	2	SGA	59.34 (32.1)							No
			AGA	68.33 (35.86)							
			SGA	85.3 (40.14)							
			AGA	66.97 (34.82)							
			SGA	103.21 (45.56)							
			AGA	66.6 (31.6)							
dos Santos Alves P. de J. ²⁶	2015	13.2 (2.5)	LBW					1/86			No
			NBW					5/86			
Huang Y. ^{a, 33}	2015	6.5 (2.5)	SGA			118.6 (105.7–222.5)					No
			AGA			76.7 (45.6–112.7)					
Blusková Z. ^{b, 19}	2014	7.2 (7.1)	SGA					0/31	3/31	1/31	No
			AGA					0/31	1/31	0/31	
Manios Y. ^{c, 14}	2014	11.2 (0.67)	SGA						1.41		BMI, Tanner stage
			AGA						(1.03–2.01)		
Giapros V.I. ¹⁵	2013	6.1 (1.3)	SGA			135 (56)					No
			AGA			97 (60)					
Kistner A. ^{d, 22}	2012	9.9 (8.5–10)	SGA						4.4 (4.3–4.5)		No
			AGA						4.4 (4.3–4.5)		
Milovanovic I. ¹⁰	2012	2	SGA	0.49 (0.08)							Sex, fat mass
			AGA	0.49 (0.09)							
Deng H.Z. ^{d, 34}	2011	6.6 (3.3)	CUG SGA	104.6 (11.4–1081.7)							Sex, age, current BMI
			NCUG SGA	65.7 (2.5–920.0)							
			AGA	90.0 (20.20–860.0)							
Tenhola S. ¹²	2010	12.2 (0.2)	SGA	0.35 (0.02)							No
			AGA	0.35 (0.02)							

Note: For quantitative outcomes, data are mean (SD), and for qualitative outcomes, n/N.

Abbreviations: ABW, adequate birth weight; AGA, adequate for gestational age; BMI, body mass index; CUG, catch-up growth; HBW, high birth weight; HOMA, homeostasis model assessment; LBW, low birth weight; NBW, normal birth weight; NCUG, non-catch-up growth; SGA, small for gestational age.

^aData are median (interquartile range).

^bThe cut-off point for HOMA-IR data was >2.7.

^cData are odds ratio (95% confidence interval).

^dData are median (range).

this review, we presented two studies^{32,34} that included SGA children with catch-up growth in their samples and discussed the inconsistency of their findings. To better understand the mediation effect of catch-up growth, future studies should go beyond simply measuring birth weight or gestational age and collect information on weight change throughout the first 2 years of life. In this scenario, although the association between being SGA and impaired glucose metabolism is biologically plausible, further prospective studies with large sample sizes, long follow-up, adequate control of confounding, and testing for an interaction with age are needed before causality can be inferred.

Although prenatal events may play an important role in the association of LBW and being SGA with impaired glucose metabolism, this relationship seems to be highly influenced by genetic factors and the postnatal environment.^{43,44} From a population perspective, given the high prevalence of LBW and SGA babies,^{7,41,42} our results are of great interest for professionals working on the prevention of chronic diseases. Birth weight is a nonmodifiable risk factor; however, at the population level, it allows for the identification of a potentially vulnerable group at risk of T2D.^{6,45} Therefore, efforts can be directed at defining optimal feeding patterns for LBW and SGA babies, promoting healthy lifestyles and identifying whether screening tests are needed.

We have conducted a systematic review of the literature regarding the association of LBW or being SGA with impaired glucose metabolism in childhood and adolescence. The main strength of our work is the scope of the review, which led to the inclusion of a large number of studies. Furthermore, this is the first meta-analysis aimed at evaluating the magnitude of the association between being SGA and the risk of T2D in childhood and adolescence, gathering the information of two large prospective cohorts. Nevertheless, some limitations must be acknowledged. First, our findings may be affected by reporting bias when we limited our search to studies published in English over the last decade. Second, this systematic review and meta-analysis was based on observational studies; thus, the results were susceptible to residual or unmeasured confounding. Third, the available data did not allow us to calculate a pool estimate for the mean differences of fasting serum glucose or insulin and the meta-analysis for HOMA-IR only included five comparisons, because very few studies reported adjusted means. Fourth, the meta-analysis for T2D, which only included two studies, may be due to the low prevalence of T2D in young populations but may also reflect a publication bias. Finally, the available data did not allow us to calculate either sex-specific or age-specific estimates.

5 | CONCLUSION

Our findings support that children and adolescents born SGA are at higher risk of having T2D. Moreover, both LBW and being SGA may be associated with lower insulin sensitivity in childhood and adolescence, reflected in higher levels of fasting serum insulin and HOMA-IR. Although the biological mechanisms underlying this association are not fully understood, the overall postnatal environment and catch-up growth have been suggested to be important mediators. Future

studies assessing the association between birth weight and impaired glucose metabolism should ensure a comprehensive collection of information about perinatal growth and consider differences by sex and age. In the meanwhile, public health efforts should be directed at identifying the optimal feeding practices for LBW and SGA babies, as well as define the most efficient protocol to control this potentially vulnerable group during the growth stage.

ACKNOWLEDGMENTS

This paper and this supplement issue on Determinants of Childhood Obesity is an ancillary endeavour of the Science & Technology in childhood Obesity Policy (STOP) project (H2020 SC2; ref.774548).

CONFLICT OF INTEREST

No conflict of interest statement.

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SUPPORTING INFORMATION

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How to cite this article: Martín-Calvo N, Goni L, Tur JA, Martínez JA. Low birth weight and small for gestational age are associated with complications of childhood and adolescence obesity: Systematic review and meta-analysis. *Obesity Reviews*. 2022;23(S1):e13380. doi:10.1111/obr.13380